

DRUG-INDUCED STATES OF
ALTERED CONSCIOUSNESS.

by

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THE DESIRE TO TAKE MEDICINE IS PERHAPS
THE GREATEST FEATURE WHICH DISTINGUISHES
MAN FROM ANIMALS.

SIR WILLIAM OSLER.

SUMMARY.SECTION I:

A brief review of the physiology of sleep and of the physiological differences between the two types of sleep, namely, rapid eye movements (REM) and orthodox (NREM) is followed by a review of the evidence of a need for each. The effects of commonly used hypnotics on sleep is reviewed with particular reference to their effects on REM sleep.

SECTION II:

General methodology, including preparation of subjects for recording in projects No. 1 and 3 is described.

SECTION III:

(A) All night recordings of EEG, EOG and EDG activity of six young, healthy male adults were carried out after administration of 10 mg. nitrazepam or 200 mg. sodium amylobarbitone each for two nights. Compared with four placebo nights, drugs shortened the delay to onset of sleep, reduced percent MT (movement) time and the number of shifts to MT and Stage 1. Sodium amylobarbitone reduced also the percent Stage 1 time. Stage 2 time was increased on drug nights but combined Stages 3 + 4 did not show any significant difference.

The drugs caused a significant reduction in the REM sleep time and prolonged the delay to onset of the first REM period. EDG activity during REM sleep and Stage 4 of NREM sleep was significantly reduced but there was no significant difference between the two drugs.

A more striking effect was the drug-induced redistribution/

of EEG stages, with Stages 3 + 4 of NREM sleep almost confined to the first half of the night. Stage REM on the other hand, was inhibited in the first two hours but was increased in the last third of the night.

(B) Both drugs given to three subjects in double doses (nitrazepam 20 mg. and sodium amylobarbitone 400 mg.) for two nights produced changes similar to those caused by small doses but more marked. With the big dose of drugs the time to onset of sleep, percent stage 1, MT time, number of shifts to stage 1 or MT, all showed a marked reduction. Stage 2 was increased. REM sleep time showed greater reduction with the big doses and delay to first REM period was also much prolonged as compared with small doses of drugs and placebo nights. EDG activity in Stage 4 and REM sleep was markedly inhibited.

The big doses also markedly affected the distribution of various sleep stages in the three thirds of the night. Most of Stages 3 + 4 of NREM occurred in the first four hours of the night and was virtually eliminated during the last third. On the other hand REM sleep was totally absent in the first third and partially suppressed in the second third of the night.

All the drug-induced abnormalities of sleep were more marked with the big dose than the small dose, thus showing a dose-effect of these drugs on the sleep of normal human subjects.

SECTION IV:

Continuous EEG monitoring was employed in a study of 127 cases of acute drug poisoning. The drugs involved were especially barbiturates (50 cases), "Mandrax" (methaqualone and diphenhydramine) in 23 cases, nitrazepam (19 cases), tricyclic antidepressants/

(10 cases) and miscellaneous drugs (25 cases). The EEG findings as seen in the initial record were classified as follows:-

- GRADE I - Alpha rhythm or predominant alpha with beta or some rare theta (20 cases).
- GRADE II - Predominantly theta with some alpha, beta or low voltage delta (17 cases).
- GRADE III - Predominantly low/high voltage delta mixed with some theta (24 cases).
- GRADE IV - Delta with or without brief isoelectric intervals (25 cases).
- GRADE V - Suppression burst activity, namely where 5-10 cps activity of several seconds duration would alternate with electrical silence (19 cases).
- GRADE VI - Near silence but with isolated and low voltage 3-7 cps waves occurring singly or bursts of half a second duration (12 cases).
- GRADE VII - An isoelectric record totally unresponsive to any stimuli (10 cases).

EEG grades I and II were associated with consciousness or drowsiness; EEG grades III and IV patients were unconscious but responded to painful stimulation. Grades V to VII were associated with deep coma and these three grades could not be distinguished clinically.

Grade VII lasting up to 28 hours was seen in 15 cases. Ten of these showed this pattern in the initial record and five developed it sometime after admission. Eleven of these 15 cases made a full clinical recovery. One of the four patients who died was a donor in the first lung transplant operation carried out in Edinburgh.

Severe/

Severe EEG abnormalities were seen particularly with barbiturates and miscellaneous groups. Nitrazepam and fenfluramine produced least change of consciousness and least EEG change even with large overdose.

Using non-parametric tests a significant correlation was found between the EEG grades and the age, clinical assessment of depth of coma, body temperature, duration of coma and blood drug levels.

SECTION V:

After recovery of consciousness following drug overdose, twelve patients transferred to psychiatric care have been studied for periods of weeks by electrophysiological recordings of all-night sleep. "Mandrax", methyprylon, nitrazepam, phenobarbitone, amylobarbitone sodium, butobarbitone, pentobarbitone, aspirin and fenfluramine cases were studied.

In the course of this study restlessness, insomnia, delirium and also EEG epileptic-type abnormalities were observed in patients in whom a high degree of tolerance and dependance had been acquired in the presence of massive concentrations of drug.

The phenomena described cannot be deemed non-specific responses to hospital admission. Restlessness at night, for example was not maximal in these patients at their entry to the study but maximal about the time the drug ceased to act. A patient who had taken a phenobarbitone overdose got more and more restless, slept less and less, and got more and more REM sleep as the three weeks to full excretion of phenobarbitone proceeded. Two cases of nitrazepam poisoning also well illustrate the same phenomena, which in their cases, reached a peak at about the/

tenth post-overdose day.

After severe poisoning with hypnotic drugs insomnia may be severe for several nights. With eventual disappearance of the drug from the blood or urine (or loss of induced EEG fast activity) intra-sleep restlessness, as indicated by frequency of shifts to Stage 1 sleep or wakefulness, and REM sleep rise to a peak. Following phenobarbitone coma of 96 hours this latter peak occurred after 3 weeks. Return to normal of intra-sleep restlessness, and REM sleep percent, took about two months. Sleep with high voltage EEG slow waves (Stages 3 and 4) was absent or low in the first two weeks after recovery of consciousness, rising to normal thereafter.

SECTION VI. (APPENDIX)

The detailed results of sleep studies on patients included in Project No. 3 are tabulated.

CO-OPERATIVE STUDIES.

The following studies, included in this thesis, were carried out jointly with -

1. The effects of hypnotics on the sleep of volunteers (Section III) - Dr. Ian Oswald.
2. Late brain recovery processes after drug overdose (Section V) - Dr. Ian Oswald.
3. Significance of flat records in acute drug intoxication (Section IV.P.) Drs. Ian Oswald and H.J.S. Matthew.
4. Fenfluramine poisoning (Section IV.P. and V).
Drs. I. Riley, J. Corson and Ian Oswald.

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I have no words adequate to express my deep sense of gratitude to Dr. Ian Oswald under whose able guidance and supervision, I had the proud privilege to work. In hours of despair, I often thought of abandoning this work. It was due to his inspiration that I have been able to finish up the work.

I am grateful to Dr. Henry Matthew, Physician-in-Charge, and Director of the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh for allowing me access to patients admitted under his care, immense support, encouragement and guidance. The staff of the unit were not only patient but sympathetic and gave invaluable assistance watching the EEG machine, particularly at such times when weariness took the better part of me.

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I shall be failing in my duty if I do not thank the entire/

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The deciphering of the manuscript and the typing of the end product of this study have been nobly borne by Mrs. Norma Dickson.

I cannot end without expressing very sincere and deep appreciation to the volunteers and patients who participated in the investigations. Their co-operation, patience and endurance contributed largely to the success of this study.

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Finally, for domestic reasons, I should add what a lot my wife has put up with. She had to cope with a husband who because he was interested in drugs and consciousness, kept most irregular hours. She has had to suffer "night starvation" on an average for four nights a week, often every night of the week and an irascible spouse recovering from sleep deprivation. All this she has tolerated with good humour and much fortitude through all the vicissitudes of life.

DESIRING NOTHING BUT TO WIN A KNOWLEDGE OF THE
TRUTH, I HAVE FRANKLY EXPLAINED MY OPINIONS,
WHICH I AM QUITE WILLING TO CHANGE WHENEVER MY
ERRORS ARE REVEALED, AND I SHALL HOLD MYSELF
ESPECIALLY OBLIGED TO ANYONE WHO FAVOURS ME
BY SHOWING THEM AND CASTIGATING ME.

STILLMAN DRAKE,
Discoveries and opinions
of Galileo.

C O N T E N T S

	<u>Page</u>
ACKNOWLEDGEMENTS	vii
CONTENTS	ix
I. <u>SLEEP AND DRUG EFFECTS</u>	1
I.A Introduction	2
I.B (i) The two kinds of sleep	5
I.B (ii) Physiological changes during the two kinds of sleep	6
I.B(iii) The need for each kind of sleep	8
I.B(iv) Measures of the two kinds of sleep	11
I.C Barbiturates	14
I.D Non-barbiturate hypnotics	16
II. <u>GENERAL METHODOLOGY FOR RESEARCH PROJECTS (1) AND (3)</u>	18
II.A Laboratories	19
II.B Preparation for recording used in projects (1) and (3)	19
II.C Analysis of the record	21
III. <u>RESEARCH PROJECT NO. 1.</u>	23
III.A Title:- THE EFFECTS OF SODIUM AMYLOBARBITONE AND NITRAZEPAM ON THE SLEEP AND AUTONOMIC FUNCTIONING OF NORMAL HEALTHY INDIVIDUALS	24
III.B Introduction	24
III.C Methods and material	25
III.D Administration of drugs	27
III.E.(i) Analysis of the records	27
III.E(ii) Measurement of electrodermogram (EDG)	28

III.E (iii)	Night's sleep	28
III.E (iv)	Three periods of night	29
III.E (v)	Statistical methods	30
III.F	Results	31
III.F (i)	Sodium amylobarbitone 200 mg. and nitrazepam 10 mg.	31
III.F (ii)	Sodium amylobarbitone 400 mg. and nitrazepam 20 mg.	35
III.F (iii)	Small and large dose of sodium amylobarbitone and nitrazepam	38
III.G	Discussion - Project No. 1	39
IV.	<u>RESEARCH PROJECT NO. 2</u>	43
IV.A	ELECTROENCEPHALOGRAPHIC CHANGES IN ACUTE DRUG POISONING	44
IV.B	Introduction	44
IV.C	Review of the literature	45
IV.D	Patients and methods	60
IV.E	Preparation for recording used in project No. 2	61
IV.F	Analysis of the record	64
IV.G.	Statistical methods	65
IV.H	Patients	66
IV.I	EEG abnormality in the initial record	69
IV.J	Age group	70
IV.K	Clinical assessment of depth of coma	70
IV.L	Temperature on admission	71
IV.M	Total period of unconsciousness	72
IV.N	Blood drug levels	73
IV.O	Barbiturate poisoning	74
IV.P	Selected case histories	78
IV.Q	Discussion - Project No. 2	124

		<u>Page</u>
V	<u>RESEARCH PROJECT NO. 3.</u>	127
V.A	Title:- FOLLOW UP STUDY OF LATE BRAIN RECOVERY OF PATIENTS AFTER THEY HAVE MADE A CLINICAL RECOVERY FROM ACUTE DRUG POISONING.	128
V.B	Introduction	128
V.C	Methods and material	131
V.D	Discussion - Project No. 3	150
VI.	<u>APPENDIX</u>	154
	<u>REFERENCES.</u>	170

1.

I: SLEEP AND DRUG EFFECTS: REVIEW

I.A.

INTRODUCTION:

In 1929, Berger, a German psychiatrist, demonstrated a primitive form of what we know as the electroencephalogram (EEG) which is the written record of electrical potentials from the brain. This method for the investigation of brain function in health and disease, named electroencephalography, has been used by clinicians, pharmacologists and neurophysiologists.

Berger (1931) himself looked for electroencephalographic signs of the central nervous actions of some drugs, such as chloroform, morphine, cocaine, amyl nitrite and scopolamine. Since then there have been many studies to determine the effects of pharmacological agents on the human brain. Such observations were usually carried out while the subject was awake or asleep during the day. Attention was first focussed on the overnight sleep when, in 1937, Loomis and his co-workers pointed to the changing characteristics of brain waves with the onset and duration of sleep. Since then innumerable studies have been devoted to studying sleep, but the field of electroencephalography contains relatively few systematic studies of the effects of drugs on the electrical activity of the brain.

This thesis is devoted to the study of electroencephalographic (EEG) effects of some hypnotics, antidepressants/

and other drugs of clinical interest on the human brain, in both clinical dosage and self-administered overdosage. The three research projects included in this thesis are:-

- (1) A study of effects of small and larger clinical doses of two common hypnotic agents on the sleep of normal healthy volunteers.
- (2) Investigation of EEG changes in patients suffering from acute drug poisoning.
- (3) Follow up study of late brain recovery of some of these patients after they have made a clinical recovery from acute drug poisoning.

Hypnotics commonly used in clinical practice are divided into barbiturates, such as sodium amylobarbitone, and non-barbiturates of which one example is nitrazepam. Both groups are in frequent clinical use but knowledge of their effects on sleep is incomplete and much of the existing work requires confirmation.

In a previous study (Haider, 1968), 200 mg. sodium amylobarbitone and 10 mg. nitrazepam were reported to have comparable effects and to be significantly better than placebo with respect to induction, maintenance and quality of sleep. As a result of a continuing interest in the effects of hypnotics on sleep and the facilities available at the Sleep Laboratory in the Department of Psychiatry at Edinburgh University, to study electroencephalographic/

electroencephalographic effects of drugs on sleep, I undertook among my studies an examination of barbiturates and nitrazepam for their effects upon normal human subjects.

Discussion of action of drugs upon sleep requires some knowledge of the gross nature of the electrical discharges recorded from the brain during sleep. It is therefore necessary to describe the electrical characteristics of human sleep.

I.B. (i) THE TWO KINDS OF SLEEP:-

The realization that there are two different kinds of sleep arose from the pioneering observations of Aserinsky, Kleitman and Dement (Aserinsky and Kleitman, 1953, 1955; Dement and Kleitman, 1957; Dement, 1958). There are available many reviews of the physiology and psychology of the states of sleep (Oswald, 1962; Jouvet, 1965; Murray, 1965; Foulkes, 1966; Hartmann, 1967; Koella, 1967; Oswald, 1968).

The two states of sleep are commonly known as NREM (non-rapid-eye-movement) orthodox, forebrain or slow wave sleep (SWS) on the one hand, and as REM (rapid-eye-movement) paradoxical, hind-brain, activated, desynchronised, or "fast" sleep on the other.

In normal young people, the first REM period does not occur till after at least 45 minutes of sleep, more generally 60 minutes or so, and occupies about 10 minutes. Usually under 30 minutes of the first two hours of sleep is taken up with REM sleep (Oswald, 1968). The rapid eye movements tend to occur in clusters and, in almost two-thirds of adults, some characteristic EEG waves herald most of these clusters. These waves of 2-3 cps have an immediately recognizable appearance and are called "saw-tooth" waves (Berger et al., 1962). The EEG in REM sleep is of low voltage, and in the cat it resembles the waking EEG (Dement, 1958)/

1958), but in man it contains much slower frequencies than in wakefulness, made up chiefly of 4-10 cps waves. A period of REM sleep in man lasts for on average about twenty minutes and there are four or five periods of REM sleep in a normal night's sleep.

Orthodox or NREM sleep, is characterized by spindles and slow waves and in man is divided into Stages 1, 2, 3 and 4 (Fig. 1) on the basis of the amount and amplitude of the slow waves, Stage 4 having the largest and slowest waves (Dement and Kleitman, 1957; Rechtschaffen and Kales, 1968). Normally Stage 3 and 4 occur in the first 3-4 hours of the night.

I. B. (11) PHYSIOLOGICAL CHANGES DURING THE TWO KINDS OF SLEEP:-

It has been shown that the two kinds of sleep also differ in their physiological accompaniments. In NREM sleep respiration and heart rate remain regular but in REM sleep they are subject to sudden fluctuations (Snyder et al., 1964). The same authors also have shown that while in NREM sleep, blood pressure remain steady, it fluctuates during REM sleep.

In NREM sleep the brain temperature tends to fall below waking levels but at the onset of REM sleep brain temperature shows a sharper rise than at the onset of awakening (Kawamura and Sawyer, 1965). Cerebral blood flow is also much greater during REM sleep than in wakefulness (Reivich et al., 1968) specially/

specially when measurements are made in the brain stem (Baust, 1967).

Oswald et al., (1963), showed that in REM sleep, brief major body movements are more frequent, yet between movements there is usually a loss of muscle tone (Berger, 1961; Jacobson et al., 1965). This profound loss of muscle tone has been attributed to inhibitory impulses acting on the anterior horn cells of the spinal cord (Pompeiano, 1967). These inhibitory impulses descend via the anterior columns of the spinal cord (Shimizu et al., 1966) and bring about loss of electrically induced reflexes (Hodes and Dement, 1965).

The penis is flaccid in NREM sleep, but during each REM period, it is erect except in a small percentage of instances often linked with concurrent dream anxiety (Fisher et al., 1965; Karacan et al., 1966).

Mental activity too differs in these two types of sleep. If subjects are wakened from NREM-sleep, they usually describe "thinking" of the day's events rather than "dreaming". If people are wakened from REM or paradoxical sleep they usually describe their immediately preceding mental life as "dreaming". (Foulkes, 1966).

In waking life electrodermal responses (EDR) occur not only in response to sudden stimuli but also spontaneously at a low rate. Oswald et al., (1959) described the presence of almost continual, spontaneous/

spontaneous EDR, in Stage 4 of NREM sleep. Broughton et al., (1965) confirmed this and reported their sporadic appearance in REM sleep.

I.B. (iii) THE NEED FOR EACH KIND OF SLEEP:-

The demonstration of two kinds of sleep might lead to the supposition that each type served a different, even though unknown function. Experimental evidence does indeed indicate a specific need for each. Dement (1960) carried out an experiment in which volunteers were wakened for a few minutes each time they began a REM period. He did this repeatedly during the night. Since REM sleep is always preceded by NREM, his volunteers got plenty of the latter kind of sleep but were deprived of REM sleep. As a result REM sleep began to appear at shorter and shorter intervals, as if they were "trying" to get the REM sleep more and more often, so that instead of having to be wakened 5 or 6 times to prevent entry into REM sleep some 20 awakenings each night became necessary. After five nights of this, they were allowed to sleep undisturbed and spent an abnormally large amount of the night in the REM sleep as if in compensation. Repeated awakening from NREM sleep had no such effect on REM sleep. Dement's finding has been amply confirmed in animal and human studies, though it may be noted here that the compensatory increase/

increase has never been found to be more than a moderate fraction of that lost, whereas in the "rebound" after withdrawal of various drugs such as hypnotics and alcohol (Oswald and Priest, 1965), Yules et al., 1966; Evans et al., 1968), the increase of REM sleep has more than exceeded both in amount and intensity the REM sleep lost during drug administration. This rebound increase has been well demonstrated in sleep studies of amphetamine withdrawal (Oswald and Thacore, 1963) when about two months were needed for sleep to return to normal.

While REM sleep rebound appears to be evidence of a "demand" for REM sleep, animal studies show the effects of repeated or prolonged REM sleep deprivation. Sexual and feeding behaviour are increased in intensity in cats continuously deprived of REM sleep up to as long as 70 days (Dement et al., 1967). In man there is evidence that selective REM sleep deprivation (Agnew et al., 1964; Clemes and Dement, 1967) causes some subtle emotional disorders, mainly irritability and lability of mood.

There is also some evidence of specific need for NREM sleep. NREM sleep is commonly divided into stages as mentioned previously. The four stages are not evenly distributed throughout the night, Stage 4 being almost confined to the first half of the night's sleep. This alone would suggest that there is some urgent priority of whatever function this stage of sleep may serve. Total sleep deprivation is followed on the first night of undisturbed sleep by an excess of Stage 4 (Berger and Oswald, 1962; Williams et al., 1964), which is suggestive of restorative priority (Oswald, 1969)/

If normal subjects are deliberately disturbed whenever they enter Stage 4, so that they become deprived of that stage, they subsequently take more of it, as if in compensation (Agnew et al., 1964) a situation analogous to REM sleep deprivation.

On the basis of the amount and amplitude of slow wave activity and changes in the arousal threshold, it can be argued that NREM sleep stages lie on a continuum of depth or possible "worth-whileness" of NREM sleep. If this were so then it would follow that loss of Stages 2 and 3 would lead to an increase in Stage 4 by way of rapid and non-specific compensation. To test this hypothesis, Dement and Greenberg (1966) restricted the sleep of subjects over a period of several nights to about 5-hours nightly (after 5 hrs. of sleep, NREM sleep is normally almost entirely made up of Stages 1, 2 and Stage 3). The procedure had the predicted effect of increasing the absolute duration of Stage 4 in the night and they suggested that Stage 4 "is worth more" than Stage 2. Similar observations have been made by others (Webb and Agnew, 1965). Physical exercise has also been observed to increase Stage 4 NREM sleep (Baekeland and Lasky, 1966). On the other hand with increasing age the amount of Stage 4 NREM sleep diminishes (Feinberg et al., 1967; Kahn and Fisher, 1969).

There is evidence that both kinds of sleep are necessary. That each may subserve a different function is evident in the suggestion by Williams and Williams (1966); "a chronic deficit in Stage REM leads to personality disorders whereas chronic loss of slow-wave sleep (i.e. Stages 3 and 4) leads to impaired performance". Studies of such effects are only in their/

their infancy, but it is obvious that if a drug were to distort the normal proportion of the two kinds of sleep, or the stages of NREM sleep alone, the effect could be regarded as an undesirable or adverse effect.

I.B. iv.

MEASURES OF THE TWO KINDS OF SLEEP:-

It is appropriate at this point to give a general outline of the technique and measures used in the sleep studies. It has become generally accepted that the results of the first night's recording should be discarded owing to a "first night effect". Agnew et al., (1966), and Mendels and Hawkins (1967), have shown that the first night of laboratory sleep contains more awake periods and less REM sleep. Both groups found an increased delay to the onset of the first REM period and to the onset of Stage 4. They also showed that there was a greater rate of change of stage of sleep.

The value of baseline nights cannot be over-emphasised, as the distribution of REM and NREM sleep is influenced by many factors apart from drugs: for example, deliberate attempts, for reward, to try to affect the distribution of the two kinds of sleep cause a positive but very small effect (Rechtschaffen and Verdone, 1964). The mere fact that a subject is asked to take tablets, even if they are only placebo, can effect the sleep stages (Hartmann, 1968, b.). It is therefore, good practice to administer dummy tablets on adaptation as well as baseline nights.

While/

While maximum information will be obtained from recording of the whole-night the most essential information may in some instances be obtainable by recording only the first 2 or 3 hours of sleep. While a subject is taking barbiturates for example, the REM time for the early part of the night is low while in withdrawal the proportion of REM sleep is very high (Oswald and Priest, 1965). In project No. 1 only the first six hours of night's sleep has been analysed as this facilitated the division of the night into three constant and equal periods of 2 hours in order to study the effects of the hypnotics on the distribution of the sleep stages throughout the night.

Where subjects are used as their own control, as in Project No. 1, there are few problems in interpreting the changes in, say, percent REM, during drug administration. In studies using patients, such as project No. 3, norms, derived from large groups of subjects have to be used in assessing change.

In the past, the only dependent variables generally measured in non-EEG studies of the effects of drugs on sleep were: the amount of sleep, time to sleep onset and sometimes a subjective measure of night's sleep. More recent work using the EEG has involved a consideration of drug effects on both kinds of sleep. However, attention has been focussed more on REM sleep/

sleep and a general pattern is emerging. It appears that the majority of drugs in clinical use will reduce REM sleep time, at least initially. If the administration of the drug is continued over a period of days, some form of "tolerance" (Oswald and Priest, 1965; Evans et al., 1968) may develop and the REM sleep time gradually approach or return to pre-drug levels.

A mean of 23 or 24 percent in a night's sleep is usually taken as a normal value for REM sleep and the published results from many laboratories have shown remarkable uniformity. Oswald (1968) reviewed the studies from various laboratories (including this laboratory) and suggested that figures for REM sleep exceeding 35 percent or under 12 percent for a total night's sleep of 7 hrs. or more should be regarded as abnormal. Normal limits have also been suggested for other variables (Dement and Kleitman, 1957; Agnew et al., 1964; Williams et al., 1966).

At the beginning of the night the normal subject enters first into orthodox (NREM) sleep. After about an hour the first REM period of paradoxical (REM) sleep with rapid-eye-movement begins. In 1963, Oswald and Thacore suggested 45 minutes as a lower limit for the delay to the first eye movement of the night from the first spindle of the night. Although this latency is negatively correlated with REM percent it is not a one-to-one relationship. The delay is increased with the administration of hypnotics when REM time is low and conversely is/

lowered when hypnotics are withdrawn and REM time high. Oswald (1968) suggested that this delay or latency is probably the most sensitive single index of altered "pressure" for REM sleep. A shortened delay has also been reported in occasional cases of severe depression (Mendels and Hawkins, 1968) or chronic insomnia, occasional cases of schizophrenia and organic dementia (Feinberg, 1967) or drug withdrawal delirium (Greenberg and Pearlman, 1967); (Evans and Lewis, 1968). It is possible that the limit set is relevant only to young adults as it is this group who have been most often studied. Feinberg et al., (1967), who have studied the elderly, report some short latencies, though Kales et al., (1967), do not. However, in any study using elderly subjects, there is greater risk in there being contamination from drugs as the proportion of the population taking sleeping pills for sleep increases markedly after the age of 45 (McGhie and Russell, 1962).

Many drugs, including alcohol, affect sleep and various studies have been reviewed by Hartmann (1965, 1966 a.) and more recently by Oswald (1968). Therefore, only drugs commonly used as hypnotics will be considered here.

I.C.

BARBITURATES:-

Oswald et al., (1963) using heptobarbitone in a dose of 400 mg., reported that the drug significantly reduced not only the REM sleep but also the number of eye movements per unit/

unit time. It decreased the frequency of shifts from stage to stage and the frequency of body movements. Baekeland (1967) in a more comprehensive study showed that pentobarbitone given as a single dose caused reduction in time to onset of sleep, less frequent body movements, fewer spontaneous awakenings, abbreviated REM epochs during the first half of the night and a general decrease in the amount of Stage REM.

Sleep studies published so far are mainly concerned with the effects of barbiturates on REM sleep and only a few deal with other sleep stages. The effects of drugs on autonomic patterns associated with different stages of sleep has received little attention. There is however, a study by Lester et al., (1968) who found that sodium quinalbarbitone (200 mg.) decreased REM percentage and increased Stage 2 percentage. There was a decrease in the number of body movements and a trend toward less waking. The drug caused inhibition of spontaneous electrodermal responses (EDG) in slow-wave sleep.

Oswald and Priest (1965) studied the effects of sodium amylobarbitone on the sleep of two adults over a period of four months. They gave 400 mg. nightly of sodium amylobarbitone for nine nights and found lessening of the initial effect of the drug. REM sleep percentages returned to pre-drug values. On increasing the dose to 600 mg. for a further nine consecutive nights, again after an initial effect the proportion of REM sleep returned to pre-drug values. On withdrawal, there were abnormally short delays/

to the first REM period associated with excess amount of REM sleep, especially in the early part of the night. It took five weeks for the return of normal (pre-drug) amounts of REM sleep. Pentobarbitone 100 mg. given for three nights also results in a similar REM "rebound" on withdrawal (Kales et al., 1968). Similar observations were made by Evans et al., (1968) with 200 mg. sodium amylobarbitone.

The withdrawal of barbiturates leads to an increase above base-line in the number of eye movements per unit time (Kales, 1969; Oswald, 1969). There is therefore, a physiological increase in REM intensity. In the immediate drug withdrawal period there is an increase in intensity of the psychic phenomenon of which REM sleep is a concomitant i.e. dreaming. At this time dreams are more vivid and frequently described as nightmares (Oswald and Priest, 1965; Kales and Jacobson, 1967; Carroll et al., 1969). Thus, in drug withdrawal there is a physiological and psychological increase in intensity of REM sleep manifest as increased amount of REM sleep, increased number of eye movements and increased intensity of dreams.

I.D.

NON-BARBITURATE HYPNOTICS:-

Like barbiturates, glutethimide 500 mg., methyprylon 300 mg., and methaqualone reduce REM sleep and withdrawal of the drug results in an excess of REM sleep (Kales et al., 1968). Meprobamate too has been reported to cause suppression of REM sleep (Freeman et al., 1965). However chloral hydrate is said to have little effect on REM sleep (Kales et al., 1968).

Oswald/

Oswald and Priest (1965) have shown that nitrazepam in a 15 mg. dose not only reduces REM sleep but also increases the delay to the first REM period. It took several weeks following withdrawal for REM sleep to return to normal. An increased delay to the first REM period has also been noted for nitrazepam by Lob et al., (1966) in 12 psychoneurotic patients. However, they did not find an overall reduction in REM sleep. Lehmann and Ban (1968) in a study of the effects of hypnotics on the sleep of ten normal volunteers found that nitrazepam prolonged the delay to onset of first REM period and reduced the total REM time in the night and Lewis (1968) has demonstrated an increase in the number of eye movements per unit time during nitrazepam withdrawal.

II. GENERAL METHODOLOGY FOR RESEARCH
PROJECTS (1) AND (3).

II. A.LABORATORIES.

The investigations were carried out in the sleep laboratories of the Department of Psychiatry, University of Edinburgh. They are sound-attenuated and ventilated. The EEG machines used were 14-channel Alvar Reega XIV and a portable 8-channel Alvar. An inter-communication system connected the bedrooms and the recording room. One of the laboratories adjoins a female ward in the North Wing of the Royal Edinburgh Hospital and is ideally suited for the recording of the sleep of the female patients without having to take them out of the ward and was used in this way for project (3).

II. B.PREPARATION FOR RECORDING USED IN PROJECTS (1) AND (3).

Silver cup electrodes were filled with electrode jelly and each one was placed on the face using adhesive plaster. Two head electrodes were affixed to the scalp with collodion. For Project (1) two more electrodes, one on the dorsum of the forearm, and the other on the palm were affixed using adhesive plaster, the selected points having been abraded beforehand, with a battery driven drill, to remove stratum corneum, thus reducing the resistance to a minimum. Electrodes were fixed in the following positions:-

- (1) One lateral and below the outer canthus of the right eye./

- (ii) One lateral to the outer canthus of the left eye.
- (iii) One above the right supraciliary margin.
- (iv) One above the left supraciliary margin.
- (v) One electrode in the middle of the forehead above the nasion.
- (vi) One on the palm of the hand on the distal end of the fifth metacarpal bone.
- (vii) One on the dorsal surface of the forearm at its distal end.
- (viii) and
- (ix) Two over the submental muscles.
- (x) and
- (xi) Two head electrodes, one to a position corresponding to F_z and the second at a point between C_z and P_z .

The wires from the palm of the hand and dorsum of the forearm (project (1)) were run along the entire length of the arm and the side of the neck and gathered together and fastened on the top of the head.

The pairs of the electrodes were connected to various channels as follows:-

Channel 1:	i and iv.	Electro oculogram (EOG)
2:	ii and iii.	Electro oculogram (EOG)
3:	x and xi.	Electroencephalogram (EEG)
4:	viii and ix.	Electromyogram (EMG) - Project (3) only.
5:	vi and vii.	Electrodermogram (EDG) - Project (1) only.

Electrode/

Electrode v was used as an earth electrode. Each subject was allocated 4 channels.

The EEG machine was run for a couple of pages to ensure an artefact-free record. Each epoch ran through the machine in 20 seconds, and therefore a whole night's record was $\frac{1}{2}$ mile long. The recording lasted from approximately 23.30 hrs. which was coincident with putting out the lights till the subjects wakened in the morning at 08.00 hrs.

II.C.

ANALYSIS OF THE RECORD:

A page by page analysis of each night's record was made by the author. Reliability of reading was increased by having some records checked by Dr. Ian Oswald. In cases where doubt rose as to the appropriate sleep stage, the particular portion of the record was discussed with Dr. Oswald and other members of the sleep laboratory. The international criteria was used for scoring each record (Rechtschaffen and Kales, 1968). Examples of various stages of sleep (Fig.1) and criteria for the sleep stages are as follows:-

- Stage 0: (Wakefulness) - The EEG contains alpha activity 9-11 cycles per second (cps) and or low voltage mixed frequency activity. Blinks may be present.
- STAGE 1: - A relatively low voltage, mixed frequency EEG without rapid eye movements (REMS). However slow rolling movements of the eyes may be present.
- STAGE 2: - This is characterised by the presence of 12-14 cps sleep spindles and K complexes on a background of relatively low voltage, mixed frequency EEG activity./

EXAMPLES OF EEG STAGES OF SLEEP

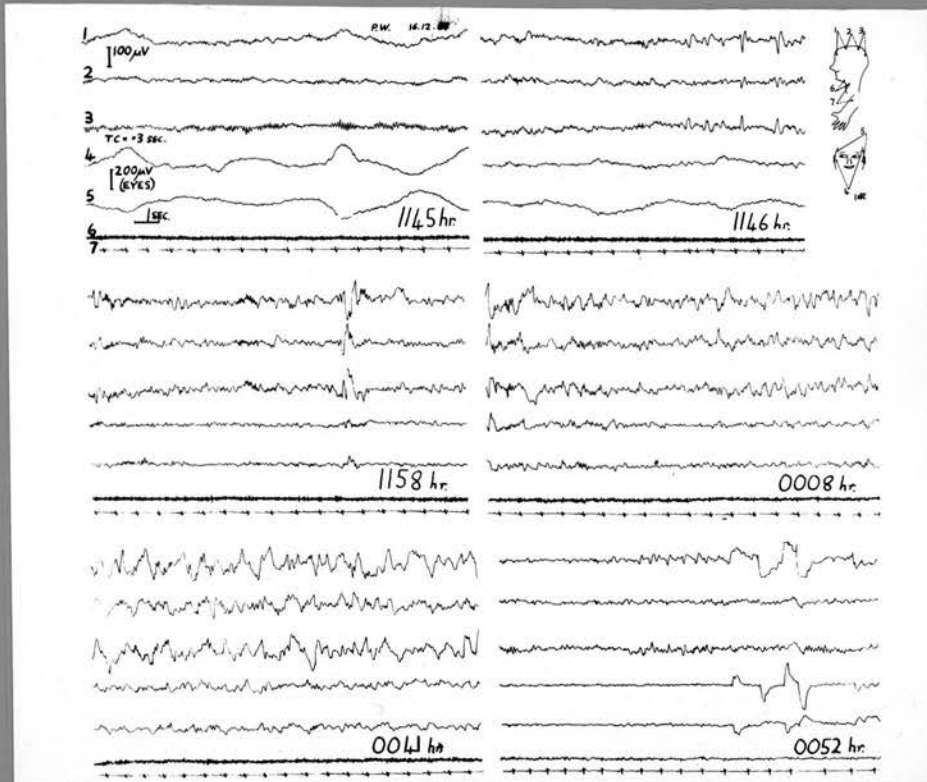


Figure 1:-

- 11.45 p.m. Awake but drowsy with alpha rhythm in channel 3 and slow, rolling eye movements revealed in channels 4 and 5.
- 11.46 p.m. Stage 1 NREM sleep. Alpha rhythm is lost and 4-6 cps waves predominate.
- 11.58 p.m. Stage 2 NREM sleep. Bursts of fast waves at about 14 cps (sleep spindles) and brief, high voltage slow wave complexes.
- 00.08 a.m. Stage 3 NREM sleep. The sleep spindles are slightly slowed in frequency and there is general slowing and increase of the background EEG.
- 00.41 a.m. Stage 4 NREM sleep. The EEG is dominated by high voltage waves at about 1 cps. The EEG potentials are visible in channels 4 and 5. Channel 6 continues as a thick trace owing to innumerable little muscle spikes. The heart rate is regular.
- 00.52 a.m. REM sleep. The EEG is of low voltage. Channels 4 and 5 reveal the large potentials of rapid eye movements (also visible in channel 1). In channel 1, just before the burst of eye movements, a little run of "saw-toothed" waves at 2-3 cps. Channel 6 now indicates much diminished muscle tone and in channel 7 the heart rate appears irregular.

- STAGE 3: - This is defined by the presence in 20-50 percent of the epoch of waves of 2 cps or slower which have an amplitude greater than 75 μ v from peak to peak. Sleep spindles may or may not be present.
- STAGE 4: - When more than 50 percent of the epoch consists of waves of 2 cps or slower waves with an amplitude of more than 75 μ v peak to peak. Sleep spindles may or may not be present.
- MOVEMENT TIME (MT): - Epoch during which the polygraph record is obscured by movements of the subject.
- STAGE REM: - This is characterized by a relatively low voltage mixed frequency EEG in conjunction with episodic REMS and low amplitude electromyogram (EMG).

The onset of sleep at the beginning of the night was defined as the presence of a clearly visible rhythmic sleep spindle of at least 0.5 sec. duration (Stage 2) and not when the subject was merely drowsy (Stage 1).

After scoring the record, the data were analysed for the following indices:-

- i. Time taken to fall asleep, in minutes since the lights were put out.
- ii. Time in minutes of sleep before the onset of first REM since subject was defined asleep (first spindle activity).
- iii. Duration in minutes of REMS during the first two hrs. of sleep. (Project 3).
- iv. Total sleep time (TST) in minutes.
- v. Duration of wakefulness in the whole night in minutes between sleep onset and final awakening (Project 3).
- vi. Number of shifts to Stage 1 (usually MT) or wakefulness from sleep during the first two hours of sleep.
- vii. Percentage Stage 1 (%S1), percentage Stage 2 (%S2), percentage stages 3 plus 4 (%S3 and %S4).
- viii. Percentage Stage REM (%SR).

SECTION III

PROJECT NO. 1.

III.A.TITLE:

THE EFFECTS OF SODIUM AMYLOBARBITONE AND
NITRAZEPAM ON THE SLEEP AND AUTONOMIC
FUNCTIONING OF NORMAL HEALTHY INDIVIDUALS.

III.B.Introduction:-

Most hypnotics depress the central nervous system and affect the reticular formation. In small doses they cause sedation; in moderate doses sleep; and in large doses a state resembling general anaesthesia. A typical example of this type of drug is the barbiturate group. Their extensive use is apparent in Ministry of Health (1964) statistics which show that barbiturates made up 8.1% of all prescriptions. At the same time overdosage by hypnotics has increased steadily as a means of attempting suicide (Kessel, 1965).

Most of the patients who attempt suicide use drugs readily available to them and these are quite often the hypnotics prescribed previously for their own treatment (Harwitz, 1969).

Barbiturates promote sleep, though suppressing REM sleep, with a concomitant increase in NREM sleep particularly Stage 2. However, even while the drug administration continues there are times when the delay to sleep onset increases and total sleep/

sleep time falls. To achieve the same effect, an increase in dose is often required. This is the familiar problem of tolerance. Stopping the drug often results in increase in delay to sleep, increased awakenings, and frightening dreams which lead to complaints of total insomnia (Evans et al., 1968).

Many clinical trials (Haider, 1968; Matthew et al., 1969) have reported comparable efficacy of nitrazepam and barbiturates. Therefore one of the aims of this investigation was to compare the effects of a standard barbiturate (sodium amylobarbitone 200 mg.,) and a commonly employed non-barbiturate hypnotic (nitrazepam 10 mg) on normal healthy volunteers and EEG measures of sleep.

It is reasonable to assume that a large dose of hypnotic, such as sodium amylobarbitone or nitrazepam would have greater effect than a smaller dose. To test this possible dose - response effect of hypnotics, a large dose of both sodium amylobarbitone (400 mg.) and nitrazepam (20 mg.) was included during the second phase of the experiment.

III.C.

METHODS AND MATERIAL:-

Six paid male volunteers, all of whom were medically and psychiatrically sound, and all over 21, were included in the study. They were requested to maintain their/

their sleep at the amount they reported as typical for themselves for three nights prior to every experimental night, to abstain from alcohol, and any other drugs, for at least one week before the start of the investigation and during the whole period of experiment, and to avoid daytime naps. They all remained in good health throughout the period of the investigation. They were told that on each experimental night before going to bed, they would be given tablets and that these would contain either a commonly used hypnotic or placebo. This reduced expectations and attendant apprehensions about the experiment. They were shown around the sleep laboratory and the procedure for each night explained. This briefing was carried out two weeks before the investigation began. The first night of recording was some two weeks later. This procedure enabled the subjects to have any second thoughts about participating.

Subjects were divided into two groups of three. Each subject was recorded according to the schedule shown in Tables 1 and 2. He attended the Laboratory on a single night at weekly intervals and took tablets on laboratory nights only.

On an experimental night, the three subjects of a group came to the laboratory, one hour before their usual bedtime. After changing into night attire, their electrodes were fixed including those for electrodermogram. The leads were taped together and run as a single cord to the head-box/

head-box at the head of the bed. This arrangement allowed a free range of movement without entanglement and minimised any annoyance to the subjects.

III.D.

ADMINISTRATION OF DRUGS:-

During the first phase of the experiment (Table 1) Group A received 10 mg. nitrazepam for two nights and Group B were given 200 mg. sodium amylobarbitone for two nights. The drugs were administered just before the lights were put out.

In the second phase, the order of drugs were reversed (Table 2) so that Group A now received 200 mg. sodium amylobarbitone for two nights and Group B had 10 mg. nitrazepam for two nights. To examine the effects of a large dose of the drugs on the same subjects, 400 mg. sodium amylobarbitone for two nights (Group A), and 20 mg. nitrazepam for two nights (Group B), were also included. In each phase the initial placebo night was treated as an adaptation night and the results discarded (the "first night" effect).

III.E. i.

ANALYSIS OF THE RECORDS:-

All the records obtained from the twenty experimental nights of this investigation (almost seven miles of paper) were read page by page. The criteria/

DISTRIBUTION OF SUBJECTS AND DRUGS
DURING FIRST PHASE OF EXPERIMENT.

GROUPS	N I G H T S(Non-Consecutive)				
	First	Second	Third	Fourth	Fifth
Group A (S1, S2 & S3)	Placebo	Placebo	Nitrazepam 10 mg.	Nitrazepam 10 mg.	Placebo
GROUP B (S4, S5 & S6)	Placebo	Placebo	Sodium Amylobarbitone 200 mg.	Sodium Amylobarbitone 200 mg.	Placebo

TABLE 1.

DISTRIBUTION OF SUBJECTS AND DRUGS
DURING SECOND PHASE OF EXPERIMENT.

GROUPS	N I G H T S (Non-Consecutive)						
	First	Second	Third	Fourth	Fifth	Sixth	Seventh
Group A							
(S1, S2, S3)	Placebo	Sod. Amylo- barbitone 400 mg.	Placebo	Sod. Amylo- barbitone 200 mg.	Sod. Amylo- barbitone 200 mg.	Placebo	Sod. Amylo- barbitone 400 mg.
Group B							
(S4, S5, S6).	Placebo	Nitrazepam 20 mg.	Placebo	Nitrazepam 10 mg.	Nitrazepam 10 mg.	Placebo	Nitrazepam 20 mg.

TABLE 2.

criteria adopted for analysis were as described previously.

III.E. ii.

MEASUREMENT OF ELECTRODERMOGRAM (EDG).

For both Stage 4 and Stage REM, the first 15 minutes, after an initial 5 minutes of first appearance of the relevant stage of sleep was used as a sample. These samples were divided into 20 sec. epochs (twelve inches long). The first REM period of the night tends to be less than the required 20 mins. The deficiency in the sample was made up from the next REM period. All samples were divided into 20 sec. epochs (twelve inches long). A map measurer with a small wheel was run along the EDG trace of the epoch.

The EDG excess in inches for each epoch was obtained by subtracting the twelve inches value for a 20 sec. epoch from the value for a 20 sec. epoch during administration. Finally average EDG excess was calculated.

III.E. iii.

NIGHT'S SLEEP:-

Oswald and Priest (1965), have suggested that although maximum information is obtainable from a whole night's sleep recording, the essential information may be/

be obtained from recording of first two hours of a night's sleep. In this investigation, only the first six hours' sleep was analysed and is sometimes referred to as the whole night's sleep.

The proportional amount of time each subject spent in each sleep stage during the course of a night's sleep is expressed as a percentage. These percentages were derived for an individual by summing across the nights for the minutes spent in a given sleep stage and total sleep time for those nights and converted to a percentage. Stages 3 and 4 have been combined for discussion of results.

III.E. iv.

THREE PERIODS OF NIGHT:-

To examine the effects of drugs on the various stages of sleep in relation to different parts of the night, each night's record was divided into three two-hour periods. Percentages expressed in relation to these three thirds refer to the percent of the total time spent in each sleep stage in each third of the night. For example, the mean percentage of six hour sleep time for REM taken across four nights on placebo is 20.25 (Table 6) of which 13.9% occurred during/

during the first third, 33.3% during the second third and 52.8% during the last third period of the night.

III.E. v.

STATISTICAL METHODS:-

In Project No. 1 two statistical tests were used. The two tailed t-test (Guilford, 1956) to test for differences between the mean amount of the various stages of sleep on placebo, the small doses of nitrazepam and sodium amylobarbitone. Analysis of variance was used to examine the difference between the EDG activity in Stage 4 and REM sleep under the three condition (Winer, 1962).

III. F.R E S U L T SIII.F.i. SODIUM AMYLOBARBITONE 200 mg. AND NITRAZEPAM 10 mg.

The immediate effect of the drugs was to decrease the delay to onset of sleep, reduce MT and the number of shifts to Stage 1 and wakefulness. Stage 2 was increased but Stages 3 and 4 were little affected. REM sleep time was decreased and the delay to onset of first REM period was increased. Spontaneous electrodermal activity occurring during Stage 4 and REM sleep was reduced. Drug induced fast activity was observed during Stage 1 and REM sleep on the drug nights.

SIX HOURS SLEEP:-

Mean percentages for six hour sleep time for the various sleep stages taken across four placebo nights and two nights each on nitrazepam 10 mg. and sodium amylobarbitone 200 mg. are presented in Tables 3, 4 and 5 respectively. The proportion of time for each sleep stage in six hour sleep and the percentage of this time spent in each third of the night, taken across placebo, nitrazepam and sodium amylobarbitone nights for all six subjects is shown in Tables 6, 7 and 8.

ONSET OF SLEEP:-

The drugs shortened the delay to sleep onset as/

MEAN PERCENTAGE OF SIX HOUR SLEEP FOR ALL STAGES OF
SLEEP TAKEN ACROSS FOUR PLACEBO NIGHTS FOR ALL SUBJECTS.

Stages of Sleep	S U B J E C T S						Mean
	S1	S2	S3	S4	S5	S6	
W	-	-	-	-	-	-	-
REM	22.37	21.38	18.56	19.49	18.12	21.57	20.25
1	6.28	4.81	12.17	8.00	12.78	12.14	9.36
2	37.49	46.95	39.73	41.56	38.93	41.21	40.97
3 & 4	24.87	22.55	23.14	25.90	26.01	20.24	23.78
MT	8.99	4.31	6.40	5.05	4.16	4.88	5.62

TABLE 3.

MEAN PERCENTAGES OF SIX HOUR SLEEP TIME FOR ALL STAGES OF

SLEEP TAKEN ACROSS TWO NIGHTS ON 10 mg. NITRAZEPAM FOR

SIX SUBJECTS.

Stages	S1	S2	S3	S4	S5	S6	Mean
W	-	-	-	-	-	-	-
REM	16.18	9.75	14.35	12.82	15.50	16.12	14.12
1	4.75	3.12	4.75	10.5	13.2	10.3	7.76
2	49.17	58.99	52.28	49.92	42.81	48.93	50.05
3 & 4	26.10	24.64	25.53	23.59	23.40	22.52	24.29
MT	3.80	3.50	3.09	3.97	5.19	2.13	3.94

TABLE 4.

MEAN PERCENTAGE OF SIX HOUR SLEEP TIME FOR ALL STAGES OF
SLEEP TAKEN ACROSS TWO NIGHTS ON 200 mg. SODIUM AMYLOBARBITONE
FOR SIX SUBJECTS.

STAGES	S1	S2	S3	S4	S5	S6	MEAN
W	-	-	-	-	-	-	
REM	11.08	16.16	9.75	13.74	11.86	17.33	13.32
1	2.15	2.46	3.11	4.60	7.10	4.83	3.96
2	54.76	56.12	58.90	52.57	51.16	53.10	54.43
3 & 4	29.91	23.11	24.74	26.95	28.01	21.63	25.72
MT	2.10	2.15	3.50	2.14	1.87	3.04	2.55

TABLE 5.

PROPORTIONAL TIME FOR EACH STAGE OF SLEEP IN SIX HOURS
OF SLEEP AND ITS PERCENTAGE DURATION IN EACH THIRD OF THE
NIGHT, TAKEN ACROSS FOUR NIGHTS ON PLACEBO FOR ALL SUBJECTS.

SLEEP STAGES	SIX HOUR SLEEP	THIRDS OF NIGHT		
		First	Second	Last
W	-	-	-	-
REM	20.25	13.9	33.3	52.8
1	9.36	44.2	34.2	21.6
2	40.97	28.2	34.7	37.1
3 & 4	23.78	47.7	30.7	21.6
MT	5.62	36.8	33.7	29.4

TABLE 6.

MEAN PERCENTAGES OF SIX HOUR SLEEP TIME FOR ALL STAGES OF SLEEP
AND PERCENT OF EACH SLEEP STAGE OCCURRING IN THREE THIRDS OF
NIGHT TAKEN ACROSS FOUR NIGHTS ON PLACEBO (P) AND TWO NIGHTS
ON 10 mg. NITRAZEPAM (N) FOR ALL THE SIX SUBJECTS.

Sleep Stages	SIX HOUR SLEEP		THIRD OF NIGHT					
	P	N	First			Second		
			P	N	-	P	N	Last
W	-	-	-	-	-	-	-	-
REM	20.25	14.12	13.9	1.7	33.3	19.9	52.8	78.3
1	9.36	7.76	44.2	38.6	34.2	35.6	21.6	25.7
2	40.97	50.05	28.2	30.9	34.7	35.7	37.1	33.3
3 & 4	23.78	24.29	47.7	47.3	30.7	36.8	21.6	15.8
MT	5.62	3.94	36.8	40.3	33.7	38.0	29.4	21.6

TABLE 7.

MEAN PERCENTAGE OF SIX HOUR SLEEP TIME FOR ALL STAGES OF SLEEP
AND PERCENT OF EACH SLEEP STAGE OCCURRING IN FIRST, SECOND AND
LAST THIRDS OF NIGHT, TAKEN ACROSS FOUR NIGHTS ON PLACEBO (P)
AND TWO NIGHTS ON 200 mg. SODIUM AMYLOBARBITONE (SA) FOR SIX
SUBJECTS.

SLEEP STAGES	SIX HOUR SLEEP			THIRD OF NIGHT					
	P	SA		FIRST			SECOND		
		P	SA	P	SA	P	P	SA	LAST
W	-	-	-	-	-	-	-	-	-
REM	20.25	13.22	13.9	3.1	3.1	33.3	22.2	52.8	74.6
1	9.36	3.96	44.2	11.5	11.5	34.2	31.4	21.6	57.1
2	40.97	54.43	28.2	27.8	27.8	34.7	29.9	37.1	42.2
3 & 4	23.78	25.72	47.7	52.1	52.1	30.7	37.8	21.6	10.0
MT	5.62	2.55	36.8	18.8	18.8	33.7	39.2	29.4	41.9

TABLE 8.

compared to placebo (Fig.2; Table 9) the reduction was more marked with sodium amylobarbitone 200 mg. ($t = 8.19$, $p < 0.01$) than with nitrazepam 10 mg. ($t = 3.65$, $p < 0.05$) but there was no significant difference between the two drugs.

EFFECTS OF DRUGS ON NREM SLEEP:-

Mean percentages for six hour sleep time for all stages of sleep on placebo, sodium amylobarbitone 200 mg. and nitrazepam 10 mg. for all six subjects taken together are presented in Table 10.

Stage 1 sleep (Fig. 3; Table 10) was significantly reduced only by sodium amylobarbitone ($t = 5.21$, $p < 0.01$), and again the difference between the two drugs was not significant. Although Stage 2 (Fig. 4; Table 10) was significantly increased both by nitrazepam ($t = 6.78$; $p < 0.01$) and sodium amylobarbitone ($t = 8.74$, $p < 0.01$) the two drugs did not show any significant difference. Combined Stages 3 and 4 (Fig. 5; Table 10), were little affected by either drug.

MT (Fig. 6; Table 10) was reduced by both drugs when compared with placebo (Sodium amylobarbitone: $t = 5.28$, $p < 0.01$; nitrazepam: $t = 3.61$, $p < 0.05$). The difference between the two drugs was also significant ($t = 4.19$, $p < 0.01$), the greater reduction being with sodium amylobarbitone. The number of shifts to Stage 1 and wakefulness (Fig. 7; Table 11) was also/

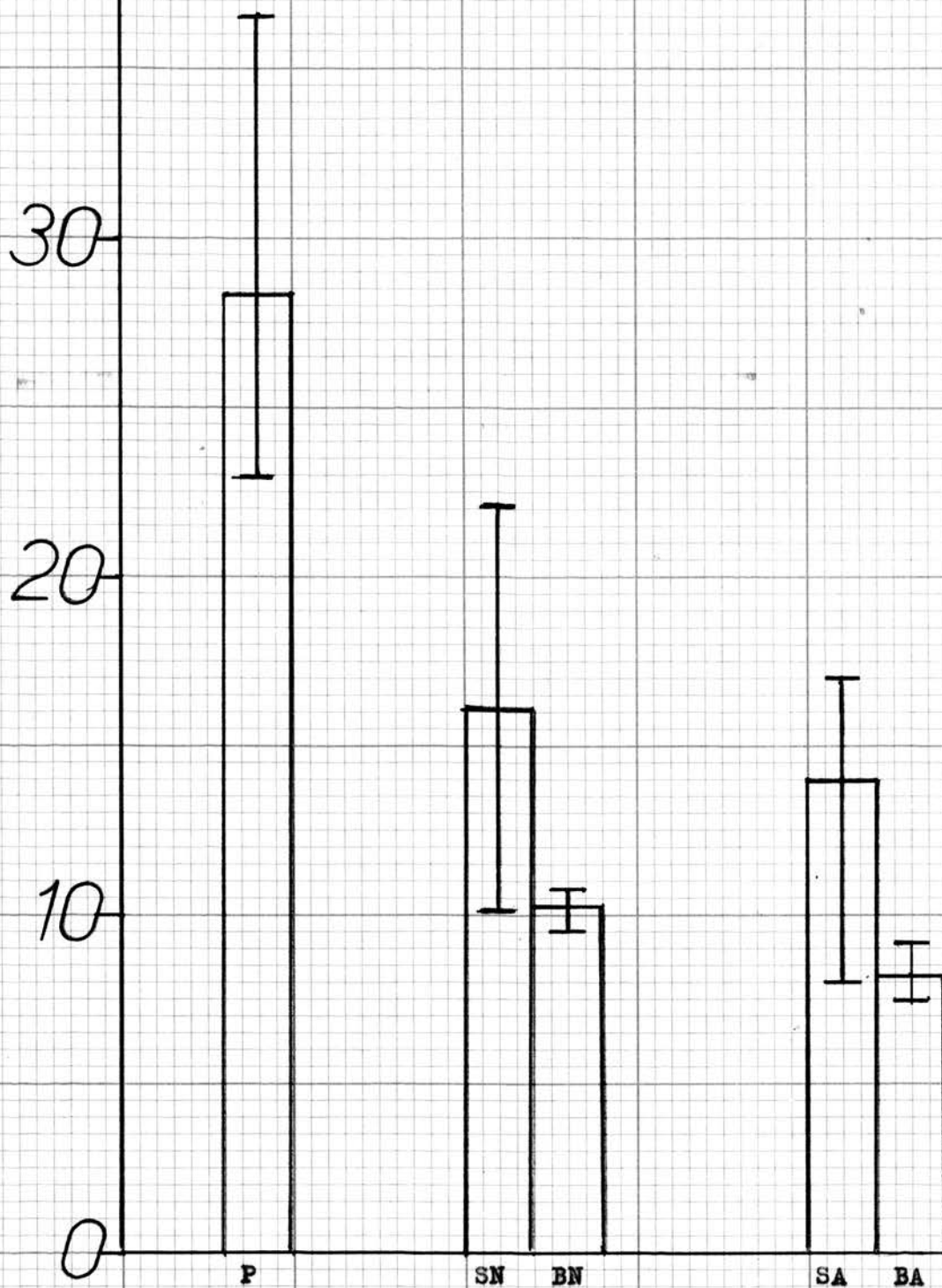


FIGURE 2.

Mean Delay to Sleep Onset in Minutes.

Placebo (P)	Nitrazepam		Sodium Amylobarbitone	
	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
N = 24	N = 12	N = 6	N = 12	N = 6

P v SN = t = 3.65; p < 0.05

P v SA = t = 8.19; p < 0.01

MEAN DELAY TO SLEEP ONSET IN MINUTES AFTER THE LIGHTS WERE PUT
OUT ON PLACEBO. SODIUM AMYLOBARBITONE AND NITRAZEPAM NIGHTS FOR
ALL THE SIX SUBJECTS.

SUBJECTS	Placebo x 4 nights.	Sod. Amylobarbitone 200 mg. x 2 Nights.	Nitrazepam 10 mg. x 2 Nights.	Sod. Amylobarbitone 400 mg. / Nitrazepam 20 mg. x 2 Nights.
S1	23.1	8.1	10.2	7.6
S2	31.5	14.5	22.1	9.2
S3	23.2	12.2	15.2	8.5
S4	27.6	17.0 °	16.0	10.8
S5	36.6	16.0	15.6	10.6
S6	28.7	17.0	19.0	9.8

TABLE 2.

MEAN PERCENTAGE OF SIX HOUR SLEEP TIME FOR ALL STAGES OF SLEEP
TAKEN ACROSS FOUR NIGHTS ON PLACEBO (P), TWO NIGHTS EACH ON
200 mg. SODIUM AMYLOBARBITONE (SA) AND 10 mg. NITRAZEPAM (SN)
FOR ALL THE SIX SUBJECTS.

SLEEP STAGES	PLACEBO	SODIUM AMYLOBARBITONE 200 mg. (SA)	NITRAZEPAM 10 mg. (SN)
W	-	-	-
REM	20.25	13.22	14.12
1	9.36	3.96	7.76
2	40.97	54.43	50.05
3 & 4	23.78	25.72	24.29
MT	5.62	2.55	3.94

TABLE 10.

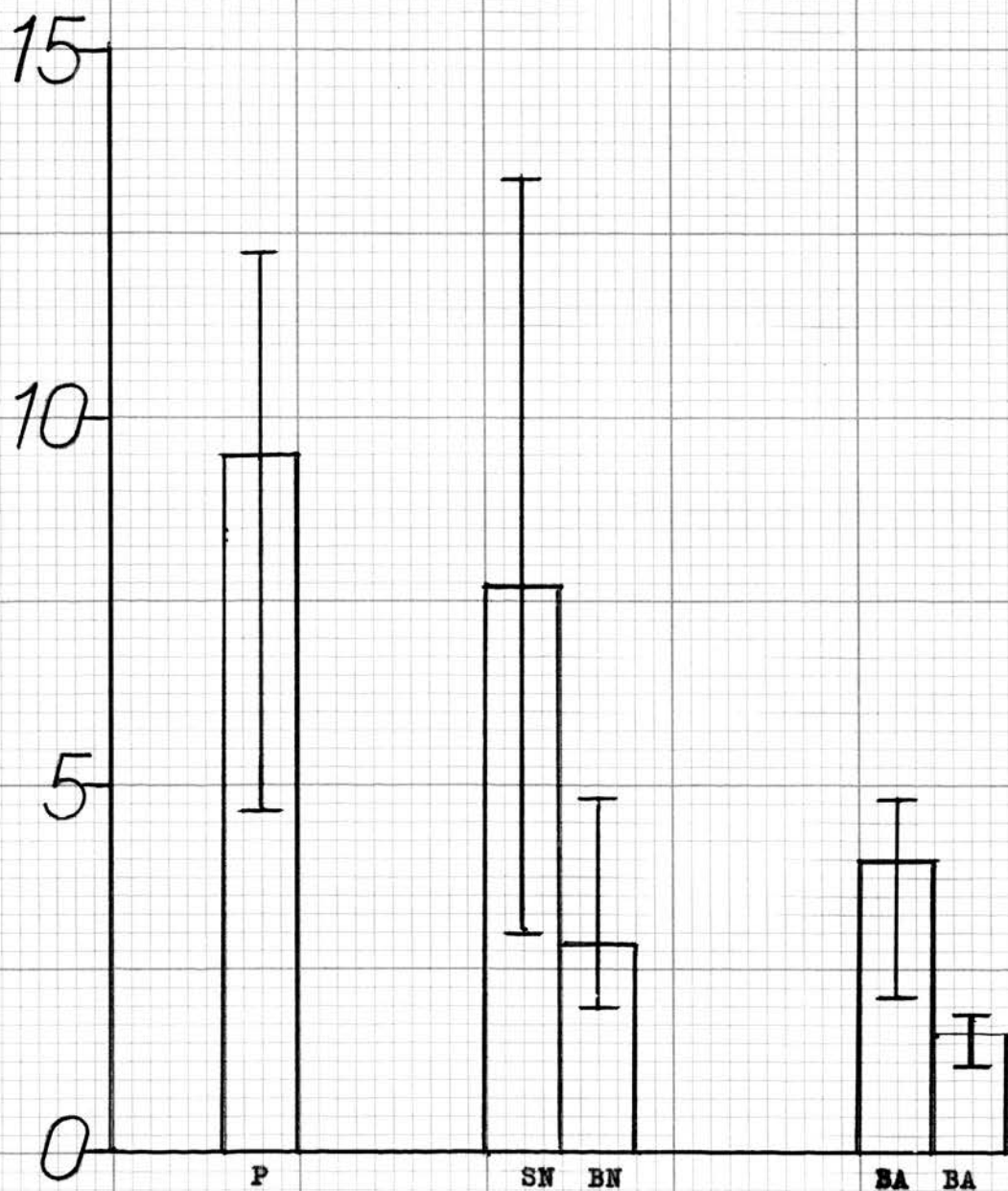


FIGURE 3.
Mean Percentage Stage 1 in First Six Hours of Sleep.

Placebo (P)	Nitrazepam		Sodium Amylobarbitone	
	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
N = 24	N = 12	N = 6	N = 12	N = 6

$P \text{ v } SA - t = 5.21; p < 0.01$

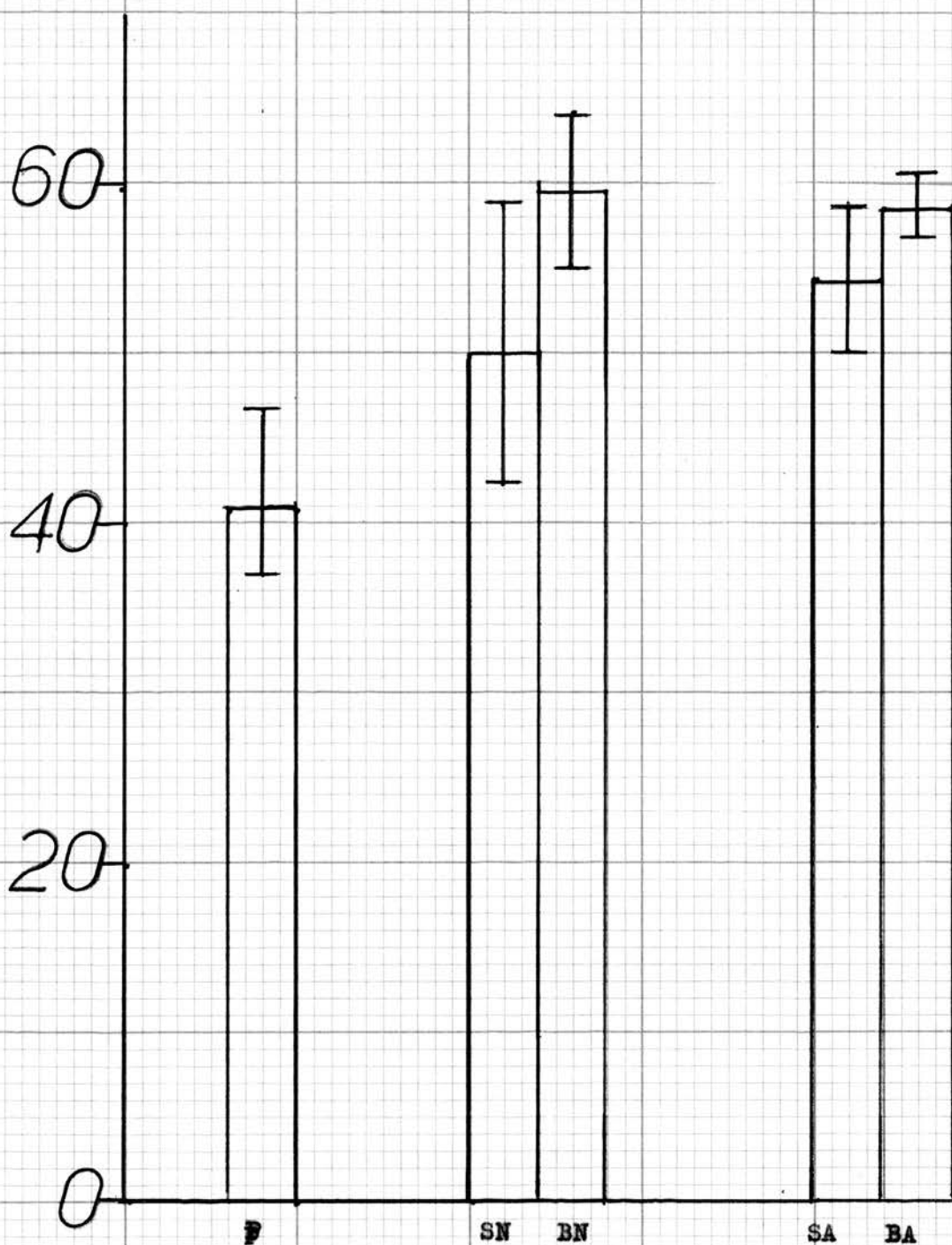


FIGURE 4.

Mean Percentage Stage 2 In First Six Hours of Sleep.

Placebo (P)	Nitrazepam		Sodium Amylobarbitone	
	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
N = 24	N = 12	N = 6	N = 12	N = 6

P v SN = t = 6.78; p < 0.01
P v SA = t = 8.74; p < 0.01

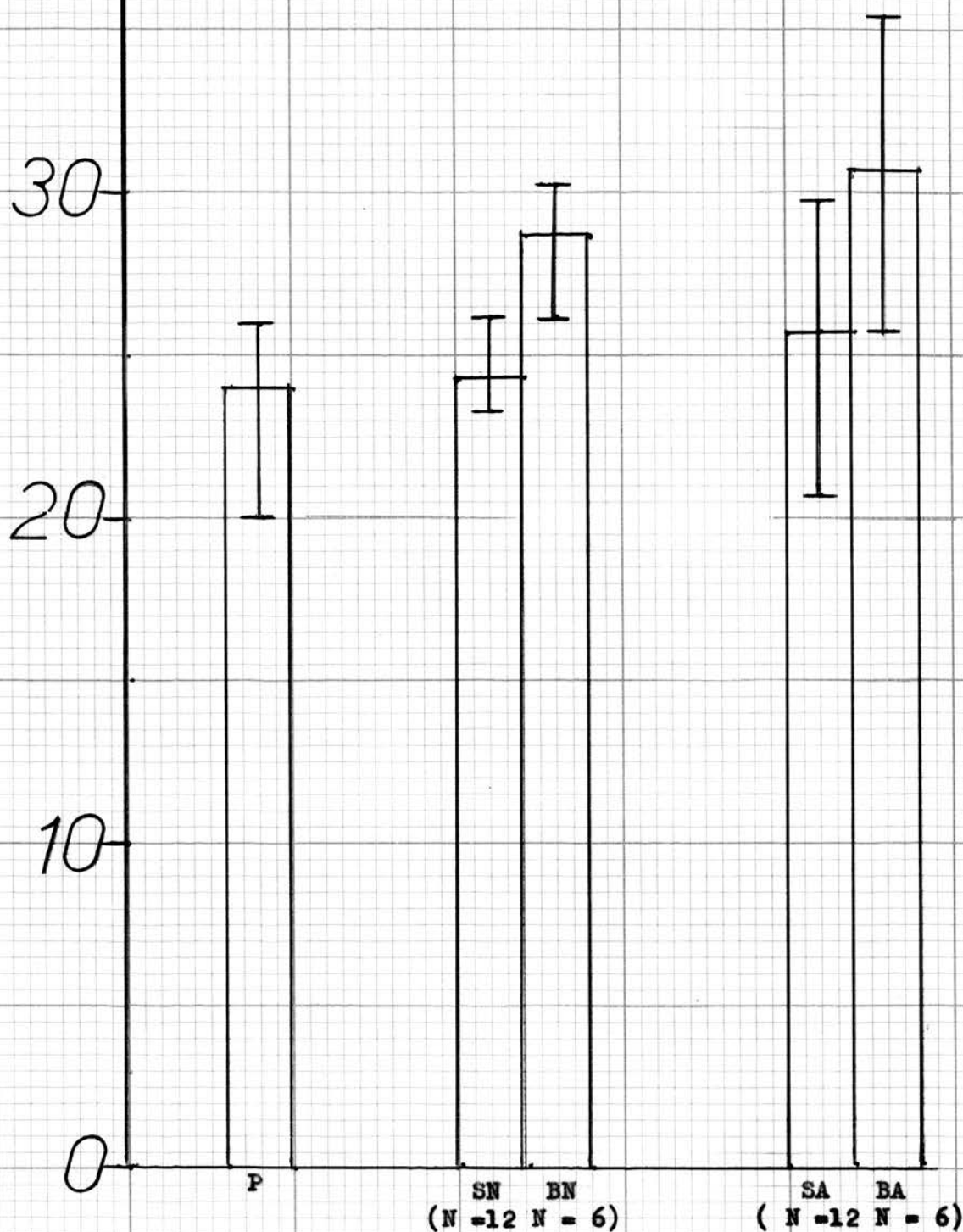


FIGURE 5.

Mean Percentage Stages 3 and 4 in First Six Hours of Sleep

Placebo	Nitrazepam		Sodium Amylobarbitone	
(P)	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
N = 24	N = 12	N = 6	N = 12	N = 6

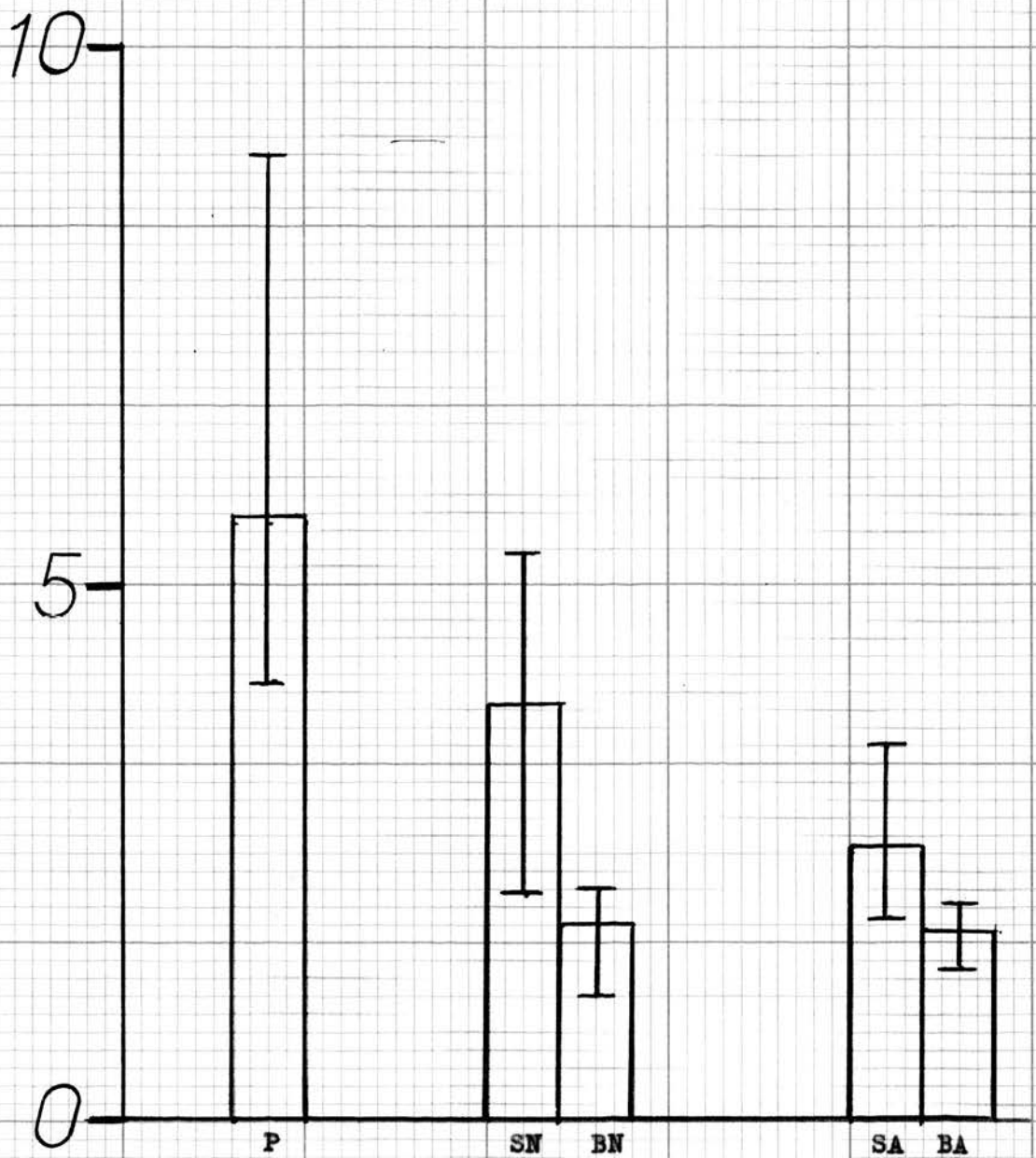


FIGURE 6

Mean Percentage MT time in first six hours of sleep.

Placebo (P)	Nitrazepam		Sodium Amylobarbitone	
	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
N = 24	N = 12	N = 6	N = 12	N = 6

$P \vee SN = t = 3.61; p < 0.05$
 $P \vee SA = t = 5.28; p < 0.01$
 $SN \vee SA = t = 4.19; p < 0.01$

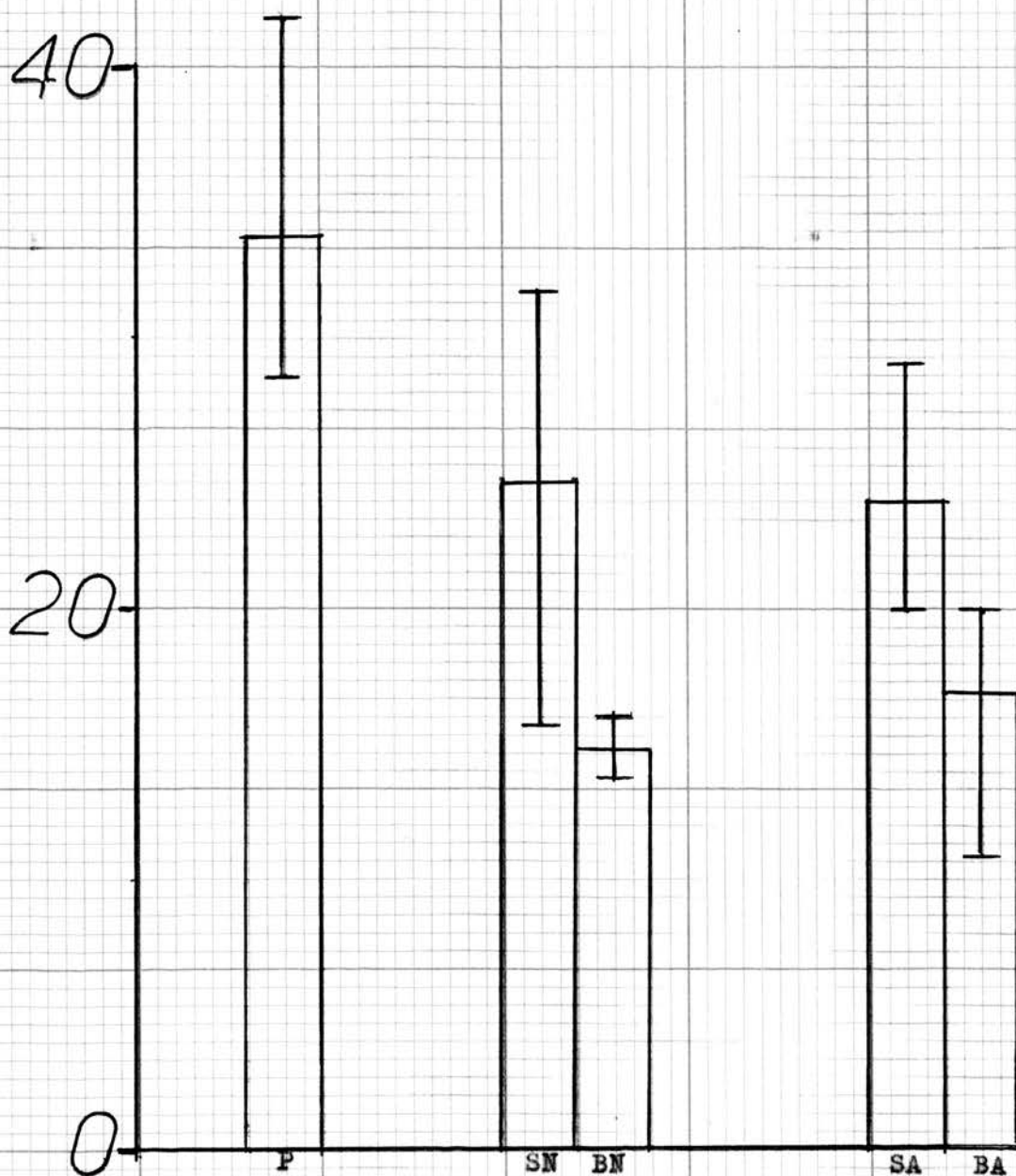


FIGURE 7.

Mean Number of Shifts to Stage 1/MT and Wakefulness
In First six hours of sleep.

Placebo (P)	Nitrazepam		Sodium Amylobarbitone	
	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
N = 24	N = 12	N = 6	N = 12	N = 6

$P \vee SN = t = 5.46 ; p < 0.01$
 $P \vee SA = t = 7.26 ; p < 0.01$
 $SN \vee SA = t = 3.09 ; p < 0.05$

NUMBER OF SHIFTS TO STAGE 1 AND WAKEFULNESS FROM SLEEP DURING
SIX HOUR SLEEP TAKEN ACROSS FOUR NIGHTS ON PLACEBO (P) AND
TWO NIGHTS EACH ON SODIUM AMYLOBARBITONE AND NITRAZEPAM FOR
ALL THE SUBJECTS.

SUBJECTS	Placebo x 4 nights	Sodium amylobarbitone 200 mg. x 2 nights.	Nitrazepam 10 mg. x 2 nights.	Sodium amylobarbitone 400 mg./Nitrazepam 20 mg. x 2 nights.
S1	42	29	32	20
S2	32	24	16	9
S3	37	26	28	12
S4	29	25	23	14
S5	33	22	26	16
S6	29	20	24	15

TABLE 11.

significantly reduced by both drugs as compared with placebo (sodium amylobarbitone: $t = 7.26$, $p < 0.01$; nitrazepam: $t = 5.46$, $p < 0.01$). The difference between the two drugs was also significant ($t = 3.09$, $p < 0.05$), the greater reduction being with sodium amylobarbitone.

EFFECTS OF DRUGS ON REM SLEEP:-

REM sleep was affected in two ways. The proportion of time spent in REM sleep (Fig.8; Table 12) was significantly reduced both by nitrazepam ($t = 6.50$, $p < 0.01$) and sodium amylobarbitone ($t = 4.91$, $p < 0.01$) but there was no significant difference between the two drugs. Secondly the delay to the onset of the first REM period (Fig. 9; Table 13) was increased from an average of 94 minutes on placebo to 130 minutes on nitrazepam 10 mg. ($t = 7.08$; $p < 0.01$) and 144 minutes on sodium amylobarbitone 200 mg. ($t = 5.32$; $p < 0.01$), but there was no significant difference between the two drugs.

THREE PERIODS OF THE NIGHT:-

Mean percentage of each sleep stage occurring in the three two-hour periods of night sleep time for all stages of sleep on placebo, sodium amylobarbitone 200 mg. and nitrazepam 10 mg. for six subjects is presented in Table 14.

In the first third of the night both drugs caused a reduction in time spent in Stages 1 and MT. Stages 2 and 3 + 4/

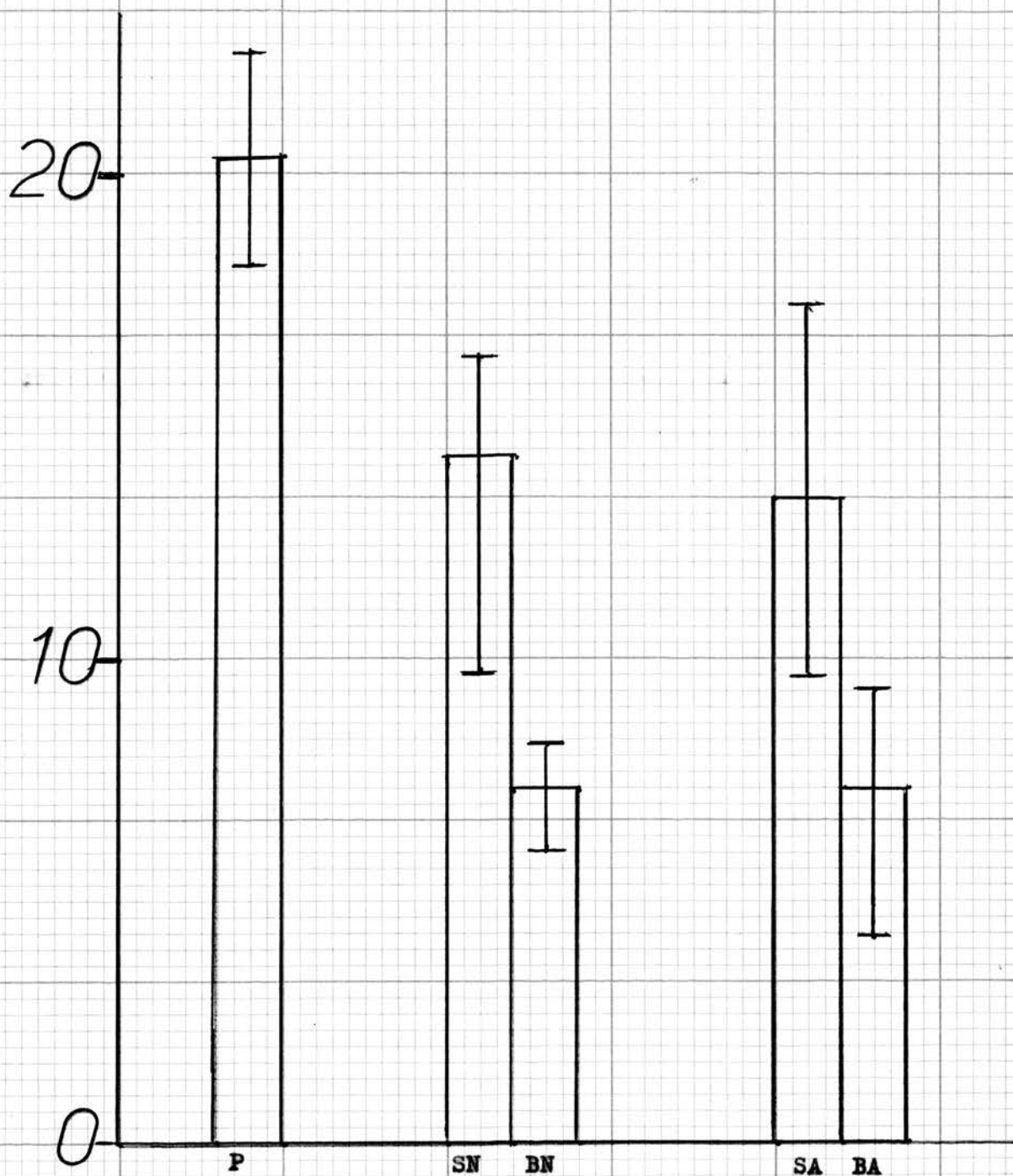


FIGURE 8

Mean Percentage REM sleep in First Six Hours of Sleep

Placebo (P)	Nitrazepam		Sodium Amylobarbitone	
	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
N = 24	N = 12	N = 6	N = 12	N = 6

P v SN = t = 6.50; p < 0.01
P v SA = t = 4.91; p < 0.01

MEAN PERCENTAGE OF SIX HOUR SLEEP TIME FOR REM SLEEP TAKEN ACROSS
FOUR NIGHTS ON PLACEBO, TWO NIGHTS EACH ON 200 mg. AND 400 mg.
SODIUM AMYLOBARBITONE AND 10 mg. AND 20 mg. NITRAZEPAM FOR ALL
THE SUBJECTS.

SUBJECTS	Placebo x 4 nights.	Sodium amylobarbitone 200 mg. x 2 nights.	Nitrazepam 10 mg. x 2 nights.	Sodium amylobarbitone 400 mg./Nitrazepam 20 mg. x 2 nights.
S1	22.37	11.08	16.18	8.16
S2	21.38	16.16	9.75	9.63
S3	18.56	9.75	14.35	4.21
S4	19.49	13.74	12.82	7.19
S5	18.12	11.86	15.50	8.16
S6	21.57	17.33	16.12	6.06

TABLE 12.

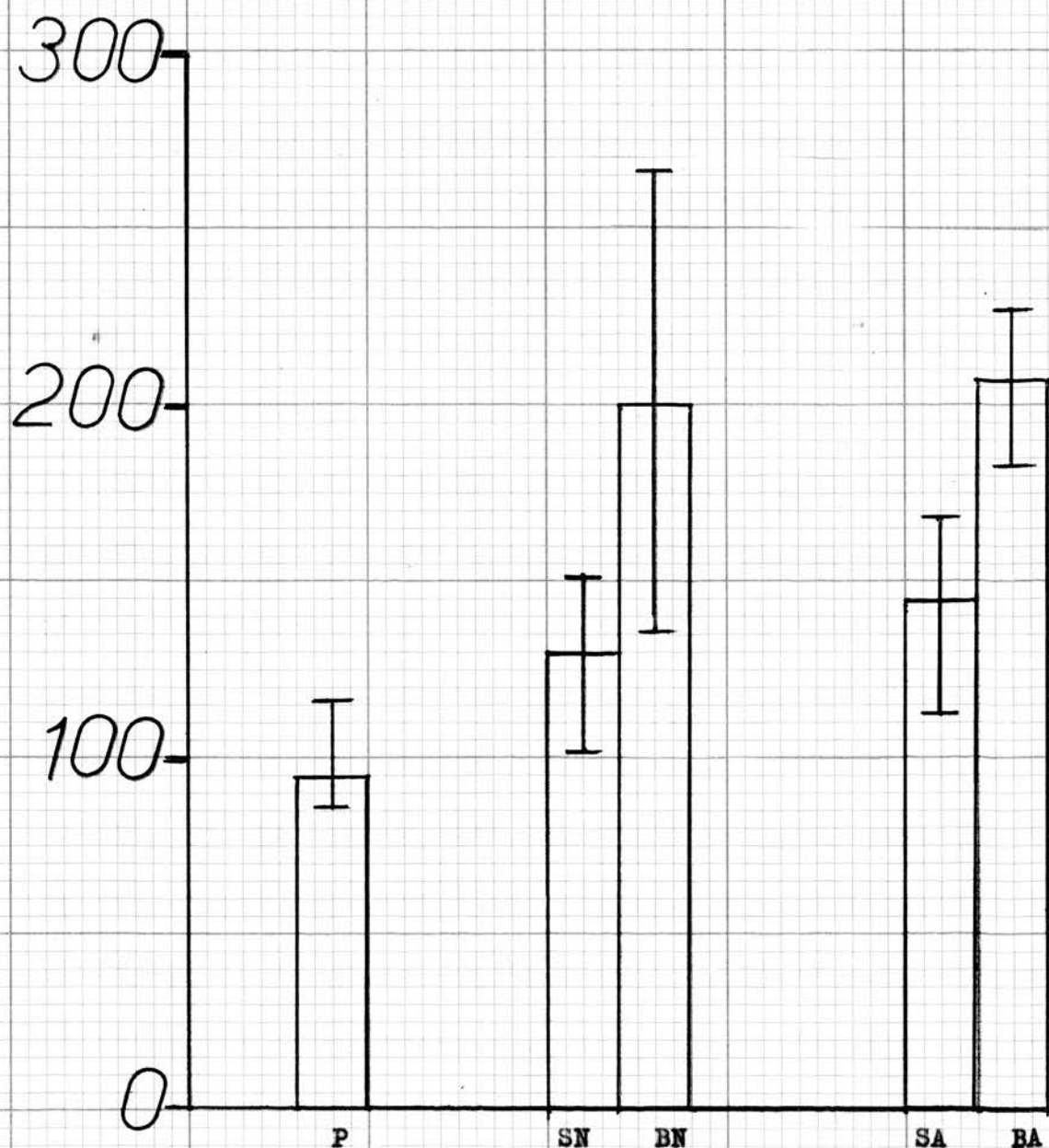


FIGURE 2

Mean Delay to Onset of First REM period in Minutes.

Placebo (P)	Nitrazepam		Sodium Amylobarbitone	
	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
N = 24	N = 12	N = 6	N = 12	N = 6

P v SN = t = 7.08; p < 0.01
P v SA = t = 5.32; p < 0.01.

DELAY IN MINUTES FROM SLEEP ONSET TO FIRST REM

PERIOD ON PLACEBO, SODIUM AMYLOBARBITONE AND

NITRAZEPAM NIGHTS.

SUBJECTS	Placebo x 4 nights.	Sod. amylobarbitone 200 mg. x 2 nights.	Nitrazepam 10 mg. x 2 nights.	Sod. amylobarbitone 400 mg./Nitrazepam 20 mg. x 2 nights.
S1	117	165	151	226
S2	90	145	146	210
S3	89	166	121	183
S4	87	133	103	136
S5	93	112	132	266
S6	87	140	125	198

TABLE 13

MEAN PERCENTAGE OF EACH SLEEP STAGE TIME OCCURRING IN THREE THIRDS
OF NIGHT SLEEP TIME FOR ALL STAGES OF SLEEP TAKEN ACROSS FOUR NIGHTS
ON PLACEBO (P) AND TWO NIGHTS EACH ON 200 mg. SODIUM AMYLOBARBITONE
(SA) AND 10 mg. NITRAZEPAM (SN) FOR SIX SUBJECTS.

SLEEP STAGES	T H I R D O F N I G H T									
	F I R S T					S E C O N D				
	P	SA	SN	P	SA	SN	P	SA	SN	LAST
W	-	-	-	-	-	-	-	-	-	-
REM	13.9	3.1	1.7	33.3	22.2	19.9	52.8	74.6	78.3	
1	44.2	11.5	38.6	34.2	31.4	35.6	21.6	57.1	25.7	
2	28.2	27.8	30.9	34.7	29.9	35.7	37.1	42.2	33.3	
3 & 4	47.7	52.1	47.3	30.7	37.8	36.8	21.6	10.0	15.8	
MT	36.8	18.8	40.3	33.7	39.2	38.0	29.4	41.9	21.6	

TABLE 14.

were little affected. During the second third, Stages 3 + 4 were increased (Fig. 10; Table 14).

Both the drugs not only reduced the total REM sleep but also affected the distribution of REM sleep in relation to three thirds of the night. It was markedly suppressed in the first third (Fig. 11; Table 14), partially suppressed in the second third and most of the night's REM sleep occurred during the last third.

EFFECT OF DRUGS ON EDG ACTIVITY:-

Spontaneous electrodermal (EDG) activity occurring during Stage 4 was measured as described previously. Mean excess EDG activity (in inches) of the first 15 minutes of the first period of Stage 4 sleep taken across four nights on placebo, two nights each on nitrazepam 10 mg. and sodium amylobarbitone 200 mg. is presented in Table 15. It was reduced by both the drugs (Fig. 12, Table 16). Analysis of variance showed a significant difference between treatments ($F = 15.05$; $df = 2, 10$; $p < 0.001$). During REM sleep too, EDG activity was reduced by both the drugs (Fig. 13; Tables 17 and 18). Analysis of variance again showed a significant treatment effect ($F = 37.33$; $df = 2, 10$; $p < 0.001$).

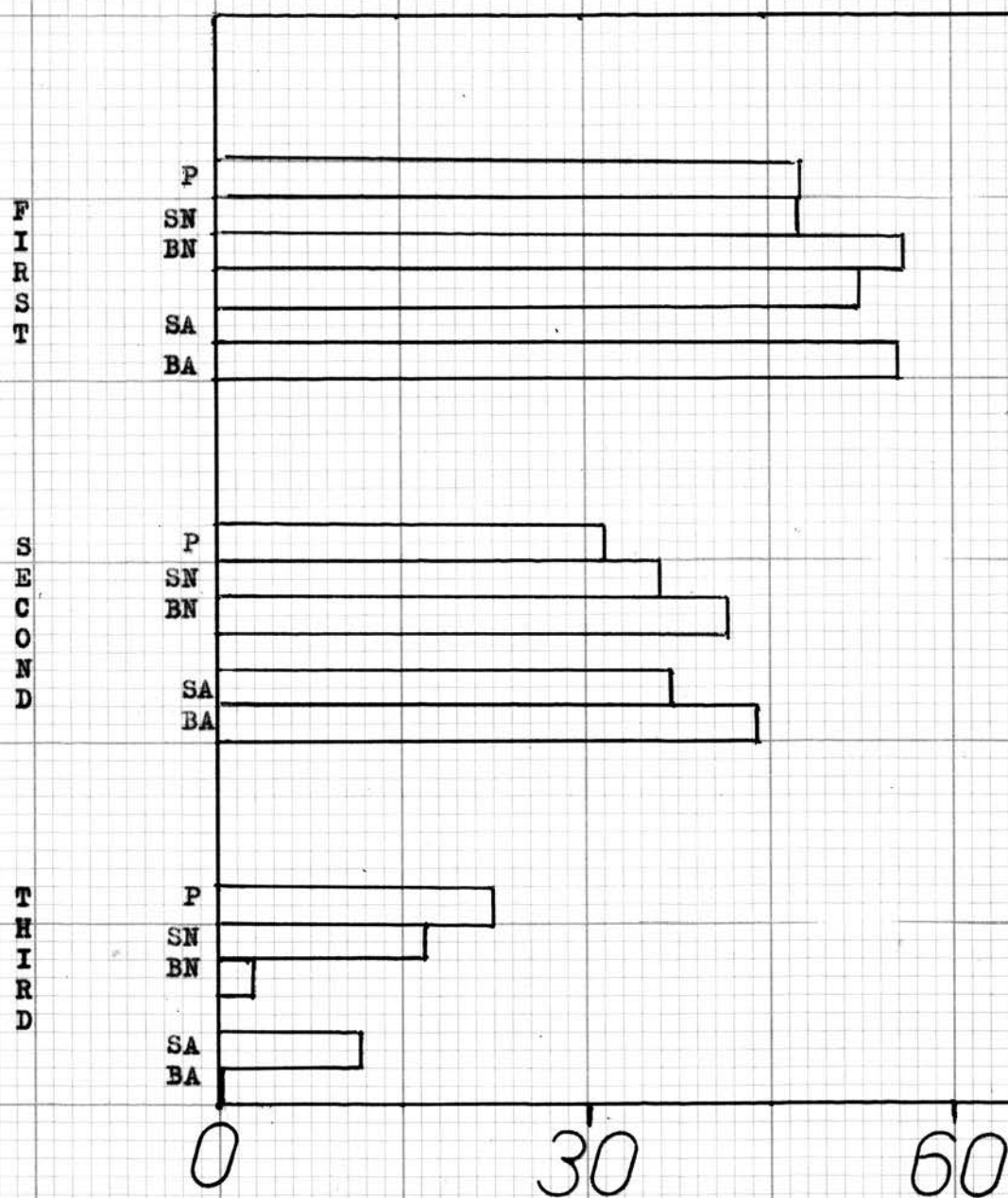


FIGURE 10.

Percentage of total stages 3 and 4 of sleep occurring in First, Second and Third Periods of night.

PERIODS OF NIGHT

	Placebo	Nitrazepam		Sodium amylobarbitone	
	(p)	10 mg. (SN)	20 mg. (BN)	200 mg (SA)	400 mg. (BA)
Nights	N = 24	N = 12	N = 6	N = 12	N = 6

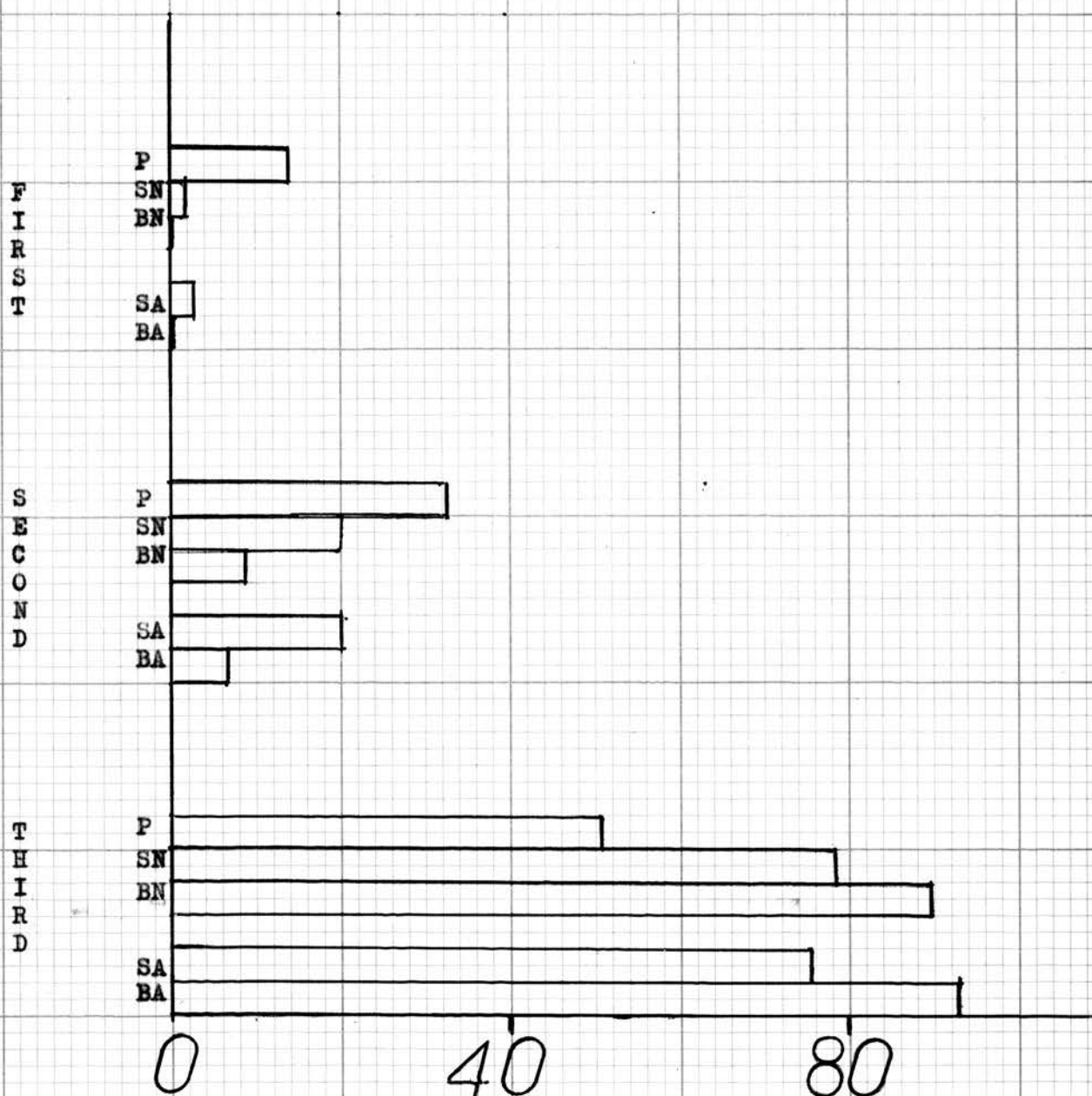


FIGURE 11.

Percentage REM sleep occurring in First, Second and Third Periods of Night.

Placebo (P)	Nitrazepam		Sodium amylbarbitone	
	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
Nights N = 24	N = 12	N = 6	N = 12	N = 6

MEAN EDG EXCESS FOR 15 MINUTES OF FIRST STAGE 4 PERIOD OF SLEEP TAKEN ACROSS
FOUR NIGHTS ON PLACEBO, TWO NIGHTS EACH ON 10 mg. AND 20 mg. NITRAZEPAM AND
200 mg. AND 400 mg. SODIUM AMYLOBARBITONE.

SUBJECTS	PLACEBO	NITRAZEPAM 10 mg.	SODIUM AMYLOBARBITONE 200 mg.	SODIUM AMYLOBARBITONE 400 mg./NITRAZEPAM 20 mg.
S1	4.74	3.64	3.72	1.27
S2	3.92	3.69	2.46	1.65
S3	4.91	4.76	3.62	1.01
S4	4.85	3.37	3.74	1.94
S5	5.74	3.79	3.83	1.76
S6	4.31	3.68	3.52	1.48

TABLE 15.

The EDG excess in inches for each epoch was obtained by subtracting the twelve inches value for a 20 second epoch from the value for a 20 sec. epoch during administration. Finally average EDG excess was calculated.

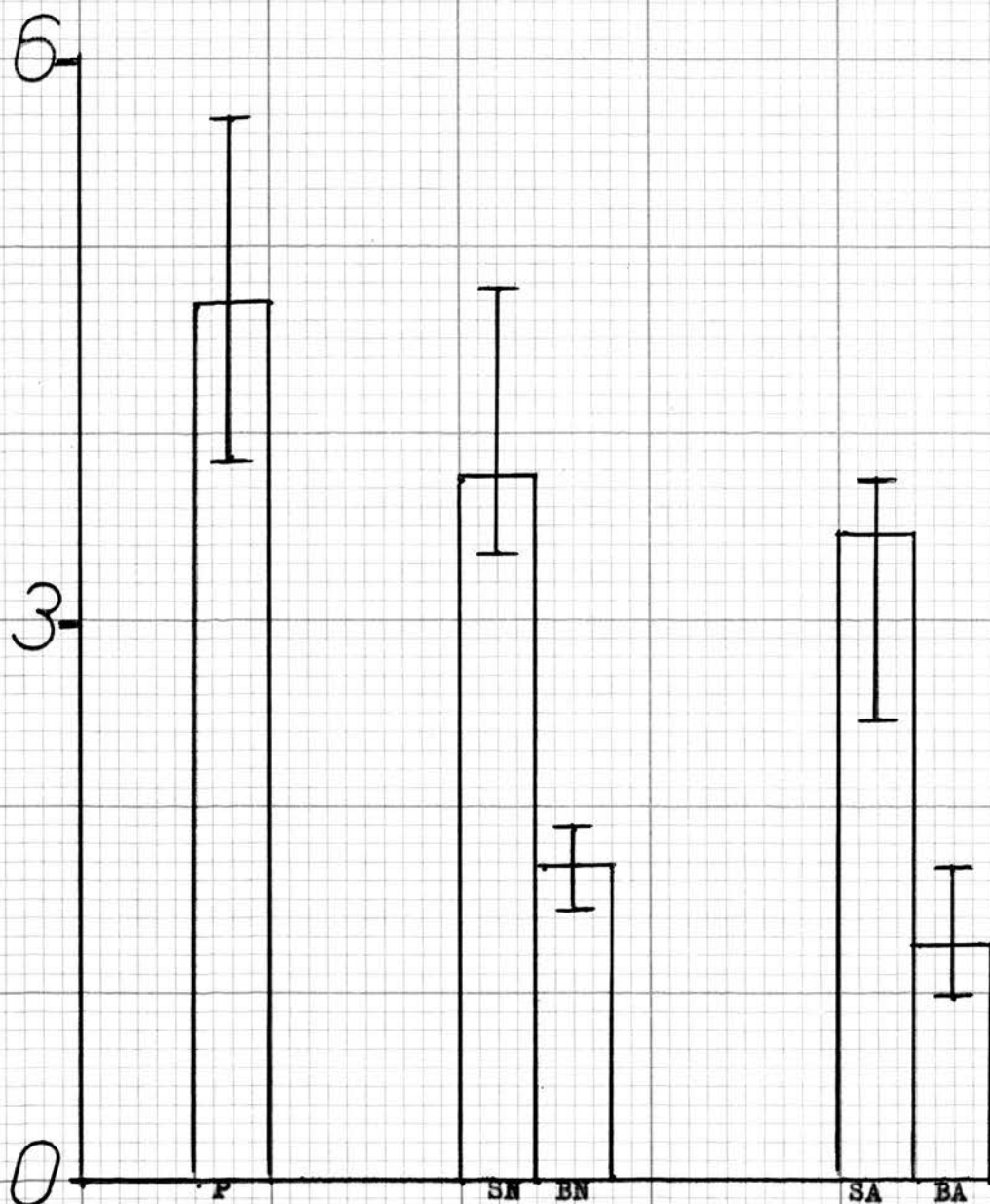


FIGURE 12.

Mean EDG excess in Inches in First 15 Minutes of Stage 4 of Sleep.

Placebo (P)	Nitrazepam		Sodium Amylobarbitone	
	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
N = 24	N = 12	N = 6	N = 12	N = 6

P v SN = $p < 0.01$
P v SA = $p < 0.01$

MEAN EDG EXCESS IN INCHES FOR FIRST 15 MINUTES OF STAGE 4 SLEEP TAKEN
ACROSS FOUR NIGHTS ON PLACEBO, TWO NIGHTS EACH ON 200 mg. SODIUM
AMYOLOBARBITONE AND 10 mg. NITRAZEPAM.

i. ANALYSIS OF VARIANCE

Source	Sums of Squares	Degrees of Freedom	Mean Square	F
Between subjects	2.49	5	0.49	0.85
Within subjects	6.90	12	0.57	
Drugs	5.13	2	2.56	15.05 *
Residuals	1.77	10	0.17	
Total	9.39	15		

ii. DIFFERENCES BETWEEN DRUGS

DRUGS	Sodium amylobarbitone 200 mg.	Nitrazepam 10 mg.	Placebo
TOTALS	20.89	22.93	28.47
Sodium amylobarbitone 200 mg.	-	2.04	7.58 **
nitrazepam 10 mg.		-	5.54 **
Placebo			-

* p 0.001
** p 0.01

Significance of differences between pairs of means
assessed by Newman-Keuls method (Winer, 1962).

TABLE 16.

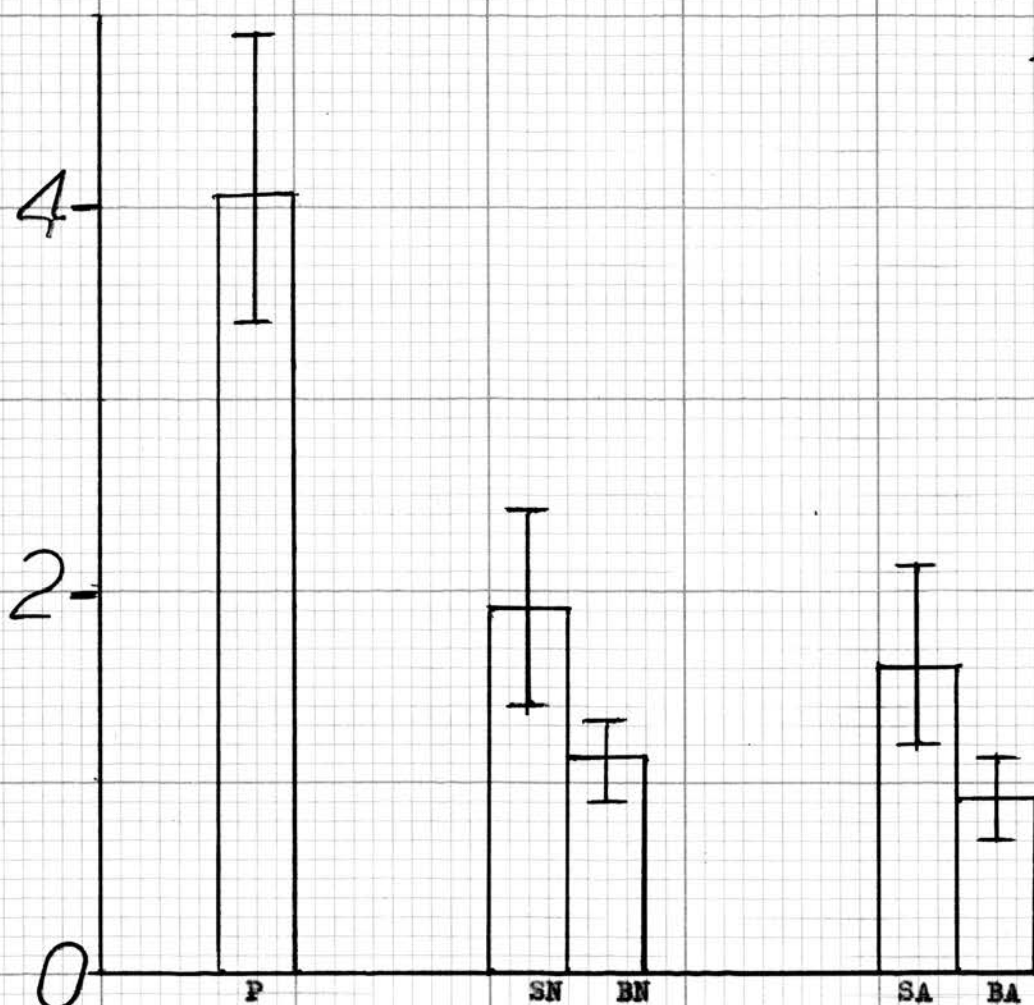


FIGURE 13

Mean E.G. excess in Inches in First 15 Minutes of REM sleep

Placebo (P)	Nitrazepam		Sodium Amylobarbitone	
	10 mg. (SN)	20 mg. (BN)	200 mg. (SA)	400 mg. (BA)
N = 24	N = 12	N = 6	N = 12	N = 6

P v SN = p < 0.01
P v SA = p < 0.01

MEAN EDG EXCESS FOR 15 MINUTES REM SLEEP DURING NIGHT. TAKEN
ACROSS FOUR NIGHTS ON PLACEBO (P). TWO NIGHTS EACH ON 200 mg.
AND 400 mg. SODIUM AMYLOBARBITONE AND 10 mg. AND 20 mg. NITRAZEPAM.

SUBJECTS	PLACEBO	SODIUM AMYLOBARBITONE 200 mg.	NITRAZEPAM 10 mg.	SODIUM AMYLOBARBITONE 400 mg./NITRAZEPAM 20 mg.
S1	3.4	2.0	1.4	0.9
S2	4.9	1.6	2.1	1.1
S3	3.8	2.1	2.4	0.7
S4	3.6	1.7	2.2	1.3
S5	3.9	1.4	1.8	0.9
S6	4.6	1.2	1.4	1.1

TABLE 17.

The EDG excess in inches for each epoch was obtained by subtracting the twelve inches value for a 20 second epoch from the value for a 20 sec. epoch during administration. Finally average EDG excess was calculated.

MEAN EDG EXCESS IN INCHES FOR FIRST 15 MINUTES OF REM SLEEP TAKEN
ACROSS FOUR NIGHTS ON PLACEBO, TWO NIGHTS EACH ON 200 mg. SODIUM
AMYOLOBARBITONE AND 10 mg. NITRAZEPAM.

i. ANALYSIS OF VARIANCE

SOURCE	Sums of Squares.	Degrees of Freedom.	Mean Square	F
Between subjects	0.85	5	0.17	0.08
Within subjects	22.91	12	1.90	
Drugs	20.17	2	10.08	37.33*
Residual	2.74	10	0.27	
TOTAL	23.76	17		

ii. DIFFERENCES BETWEEN DRUGS

DRUGS	Sodium amylobarbitone 200 mg.	Nitrazepam 10 mg.	Placebo
TOTALS	10.0	11.3	24.2
Sod. Amylobarbitone 200 mg.	10.0	1.3	14.2 **
Nitrazepam 10 mg.	11.3	-	12.9 **
Placebo	24.2	-	-

* p 0.001 Significance of differences between pairs of means assessed
** p 0.01 by Newman-Keuls method (Winer, 1962).

TABLE 18.

III.F.ii.SODIUM AMYLOBARBITONE 400 mg. AND NITRAZEPAM 20 mg:

During the second phase of the investigation, an exploratory study of large doses of both sodium amylobarbitone (400 mg.) and nitrazepam (20 mg.) was carried out. Group A subjects (S1, S2 and S3) were given 400 mg. sodium amylobarbitone (BA) on 2nd and 7th night (Table 2). Similarly Group B subjects (S4, S5 and S6) were given 20 mg. nitrazepam (BN) on the 2nd and 7th nights (Table 2). On nights 4 and 5 the subjects received the smaller doses of the drugs.

Both drugs in the higher doses shortened the delay to sleep onset (Fig. 2), decreased the time spent in Stages 1 (Fig. 3) and MT and reduced the number of shifts to Stages 1 (MT) and wakefulness. Stages 2 (Fig. 4) and 3 + 4 were increased (Fig. 5), REM sleep time was reduced (Fig. 8) and the delay to onset of first REM period increased (Fig. 9). EDG activity both in Stage 4 (Fig. 12) and REM sleep (Fig. 13) was suppressed. Both drugs induced EEG fast activity (18-20 cps) activity during Stages 1 and REM.

SIX HOUR SLEEP:-

Mean percentage of six hour sleep time for all stages of sleep taken across two nights each on sodium amylobarbitone 400 mg. (BA) and nitrazepam 20 mg. (BN) for three subjects is presented in Table 19.

A/

MEAN PERCENTAGE OF SIX HOUR SLEEP TIME FOR ALL STAGES OF SLEEP
TAKEN ACROSS TWO NIGHTS ON 400 mg. SODIUM AMYLOBARBITONE IN
GROUP A (S1, S2, S3) AND 20 mg. NITRAZEPAM IN GROUP B. (S4, S5, S6).

STAGES	2 Nights x 400 mg. SODIUM AMYLOBARBITONE			2 Nights x 20 mg. NITRAZEPAM		
	S1	S2	S3	S4	S5	S6
W	-	-	-	-	-	-
REM	8.16	9.63	4.21	7.19	8.16	6.06
1	1.63	1.28	1.85	2.10	3.94	2.06
2	58.10	61.25	56.89	59.31	55.61	64.09
3 & 4	30.76	25.85	35.16	29.31	30.10	26.09
MT	1.35	1.99	1.89	2.09	2.19	1.16

TABLE 19.

A comparison of mean percentages of six hour sleep time for all stages of sleep and percent of each sleep stage time occurring in three two-hourly thirds taken across four nights on placebo and two nights on sodium amylobarbitone 400 mg. (BA) for group A subjects is shown in Table 20 and nitrazepam 20 mg. (BN) for three subjects of group B is shown in Table 21.

EFFECTS OF DRUGS ON NREM SLEEP:-

Both drugs shortened the delay to sleep onset (Fig. 2; Table 9) from an average of 28.4 minutes on placebo to an average of 9.4 minutes on drug nights. The amount of Stage 1 of sleep was reduced (Fig. 3; Tables 20 and 21) from an average of 9.4% on placebo nights to an average of 2.1% on drug nights. MT time was reduced (Fig. 6) from an average of 5.6% on placebo nights to 1.8% on drug nights, while Stage 2 was increased (Fig. 4) from an average of 41.0% on placebo nights to 59.2% on drug nights. Also increased was Stages 3 + 4 (Fig. 5; Tables 20 and 21) from an average of 23.8% on placebo to 29.6% on drugs. The total number of shifts to Stage 1 (MT) and wakefulness was also reduced (Fig. 7; Table 11) from an average of 34 on placebo to 16 on drug nights.

EFFECTS ON REM SLEEP:-

The percent REM sleep (Fig. 8; Table 12) was markedly reduced from an average of 20.3% on placebo nights to 7.2% on drug nights. A second REM sleep change was the concomitant/

COMPARISON OF MEAN PERCENTAGES OF SIX HOUR SLEEP TIME FOR ALL STAGES OF SLEEP AND PERCENT OF EACH SLEEP STAGE TIME OCCURRING IN THREE TWO HOURLY PERIODS, TAKEN ACROSS FOUR NIGHTS ON PLACEBO (P) AND TWO NIGHTS ON 400 mg. SODIUM AMYLOBARBITONE (BA) FOR THREE SUBJECTS.

SLEEP STAGE	SIX HOUR SLEEP			T H I R D O F N I G H T							
				First				Second			
				P		BA		P		BA	
	P	BA		P	BA	P	BA	P	BA	P	BA
W	-	-	-	-	-	-	-	-	-	-	-
REM	20.3	7.3	13.9			33.3	6.3			52.8	93.7
1	9.4	1.6	44.2		8.4	34.2	30.2			21.6	61.4
2	40.9	58.8	28.2		32.4	34.7	36.8			37.1	30.8
3 & 4	23.8	30.6	47.7		56.3	30.7	43.7			21.6	-
MT	5.6	1.7	36.8		9.2	33.7	32.4			29.4	58.4

TABLE 20.

COMPARISON OF MEAN PERCENTAGES OF SIX HOUR SLEEP TIME FOR ALL STAGES OF SLEEP AND PERCENT OF EACH SLEEP STAGE TIME OCCURRING IN THREE PERIODS TAKEN ACROSS FOUR NIGHTS ON PLACEBO (P) AND TWO NIGHTS ON 20 mg. NITRAZEPAM (BN) FOR THREE SUBJECTS.

SLEEP STAGES	SIX HOUR SLEEP			T H I R D O F N I G H T					
				First			Second		
	P	BN		P	BN		P	BN	BN
W	-	-	-	-	-	-	-	-	-
REM	20.3	7.1	13.9	33.3	-	8.4	52.8	91.6	
1	9.4	2.7	44.2	34.2	10.1	23.3	21.6	66.6	
2	40.9	59.7	28.2	34.7	38.2	34.1	37.1	27.7	
3 & 4	23.8	28.6	47.7	30.7	56.4	41.1	21.6	2.5	
MT	5.6	1.8	36.8	33.7	14.5	29.2	29.4	56.3	

TABLE 21.

increase in the delay to onset of first REM period (Fig.9; Table 13) from an average of 94 minutes on placebo to an average of 203 minutes on drug nights.

THREE PERIODS OF THE NIGHT:-

Both drugs affected the distribution of sleep stages in relation to three thirds of night. In the first third both drugs (Tables 20 and 21) caused a reduction in time spent in Stages 1 and MT. Stages 3 + 4 (Fig.10) occurred in the first and second thirds and were almost absent from the last third.

REM sleep was completely suppressed in the first third of the night (Tables 20 and 21), partially suppressed in the second third; most REM was seen in the last third of the night (Fig. 11).

EFFECTS OF DRUGS ON THE EDG ACTIVITY:-

Spontaneous EDG activity occurring during Stage 4 (Fig. 12) was reduced both by sodium amylobarbitone (400 mg.) from an average of 4.74 inches on placebo nights to 1.31 inches on drug night and by nitrazepam (20 mg.) to an average of 1.72 inches.

A similar reduction was observed in EDG activity during REM sleep (Fig. 13; Table 17).

III.F.11.SMALL AND LARGE DOSE OF SODIUM AMYLOBARBITONE AND NITRAZEPAM.

In the preceding account of the effects of large doses of the drugs, statistical tests were not possible owing to the smallness of the samples. However, the tables and figures reveal that the effect of the large doses was in the same direction as the significant effect of the small doses and that without exception the mean effects of the large doses exceeded the mean effect of the small doses. Thus Tables 9, 11, 12, 13, 15 and 17 show that for every individual the mean effect of the large dose exceeded the mean effect of the small dose with respect to delay to sleep onset, shifts to Stage 1 and wakefulness, total REM sleep time, delay to the first REM period, EDG activity in Stage 4 and Stage REM. Fig. 8 indicates the greater effects of the large doses on REM sleep duration. In view of the consistency of the trends with larger doses we may conclude that in both drugs the effect of the larger dose on the sleep variables exceeded the significant effect of the small dose. No obvious differences between the two drugs were to be seen.

III.G.D I S C U S S I O NPROJECT No.1.

Comparison of 200 mg. sodium amylobarbitone and 10 mg. nitrazepam on EEG sleep, shows that both drugs caused a significant reduction in time to onset of sleep, which is consistent with the similar reduction by heptabarbitone (Oswald et al., 1963) and nitrazepam (Lehmann and Ban, 1968). Stage 1 of NREM sleep was reduced by both drugs as compared with placebo, though the difference was significant only on sodium amylobarbitone nights. Stage 2 was significantly increased by both drugs, a finding similar to that reported by other workers (Baekeland, 1967; Lester et al., 1968).

Combined Stages 3 + 4 were not significantly affected by either drug. This does not agree with the findings by Lechner (1965) who reported a decrease in Stages 3 + 4 with nitrazepam.

The reduction of MT time and number of shifts to Stage 1 and wakefulness during the night caused by both the drugs is consistent with the similar reduction by heptabarbitone (Oswald et al., 1963) and by quinalbarbitone (Lester et al., 1968).

Both/

Both drugs not only reduced the REM sleep proportion per night but also significantly prolonged the delay to onset of first REM period. This supports the similar finding by Lob et al., (1966) and confirms the findings of Oswald and Priest (1965).

The EDG activity during Stage 4 and REM was significantly decreased by both drugs. This is consistent with the findings of Lester et al., (1968) who reported a significant reduction in EDG activity during REM sleep with a single dose of 200 mg. sodium quinalbarbitone. In the present investigation, while both sodium amylobarbitone and nitrazepam caused a significant reduction in EDG activity, there was no difference between the two drugs. This in fact, is a notable feature of this investigation.

A comparison of the three two-hourly periods of the night showed that both drugs caused changes in the distribution of sleep stages. Although there was a reduction in absolute values of REM sleep time on drug nights, the distribution of REM sleep time was especially changed. These findings are similar to those reported by Lester et al., (1968) who found a shift towards the first half of the night in the distribution of Stages 3 + 4 and inhibition of REM sleep in the first half.

It is concluded that both 200 mg. sodium amylobarbitone and 10 mg. nitrazepam affect the sleep of normal human subjects and both produce similar abnormalities. The two drugs also resemble each other in the extent to which they produce changes, the only exceptions being that 200 mg. sodium amylobarbitone/

caused greater reductions in MT time and shifts to Stage 1 or MT. Both drugs induce similar abnormal fast activity at about 18 cps in the EEG during Stage 1 and REM sleep.

The second phase of this investigation was an exploratory study of larger doses of both drugs. It is accepted that the experimental design was not ideal as it does not give enough numbers for comparison by normally applicable statistical methods, but as the magnitude of work and volume of data that must be collected from even one subject-night, is considerable, and in view of consistency of results with large doses in this study it was not considered worthwhile to do a more extensive study of the bigger dose of the drugs such as used in this project.

The results show that both sodium amylobarbitone 400 mg. and nitrazepam 20 mg. shortened the delay to sleep, reduced the Stage 1 time, MT time and the number of shifts to Stage 1 or MT compared to placebo nights. Stages 2 and Stages 3 + 4 were increased. From the tables and histograms it is obvious that both drugs have caused these effects to a greater degree than the smaller doses of these drugs.

REM sleep time on the drug nights was reduced and the delay to the onset of the first REM period was also prolonged. These changes were more marked with the big dose.

EDG/

EDG activity occurring during Stage 4 and REM sleep was also depressed, the depression being more marked with the bigger doses of the drugs as compared with the placebo and the small dose.

Therefore, nitrazepam and sodium amylobarbitone did not allow normal sleep physiology in healthy subjects. The changes produced were related to the dose. Both drugs in small doses showed similar changes and these changes were without exception greater when larger doses were used.

IV. RESEARCH PROJECT NO. 2.

IV.A.

**TITLE: ELECTROENCEPHALOGRAPHIC CHANGES IN
 ACUTE DRUG POISONING.**

IV.B.

Introduction:- Recent progress in the field of experimental and clinical psychopharmacology has made available a large number of psychotropic drugs and has made possible their wide range application in the treatment of psychiatric disorders. At the same time the number of cases of self-poisoning being admitted to the Poisoning Treatment Centre is also rising and accounts for almost 10% of all acute medical admissions to certain general hospitals (Matthew, 1966). Figures of yearly admissions of poisoned patients to the Royal Infirmary, Edinburgh (Matthew and Lawson, 1967) showed a sharp rise in incidence of poisoning from 120 admissions in 1948, to 340 in 1958 and 1067 in 1968. The same authors reported that 80% of their patients indulged in self-poisoning. A recent report from the same centre (Matthew et al., 1969) has shown an increase in the incidence of self-poisoning to 95%. The epidemic nature of acute non-fatal poisoning has been highlighted in a recent publication (Central and Scottish Health Services Councils, 1968).

 An important factor in the increase of acute drug poisoning is the ready availability of drugs. In recent years, the tranquillizing and antidepressant drugs have joined the hypnotics as common agents in suicidal attempts. Many of these drugs/

drugs, at high doses, can produce CNS depression, loss of consciousness and even death. The majority of the patients are conscious on admission, about 1/5th being unconscious (Matthew et al., 1969). Twenty one percent of poisoned patients require resuscitation on arrival at the hospital (Jenkin et al., 1969). Burston (1969) reported that 25.5% of cases of self-poisoning admitted to the hospital were "severely poisoned and would possibly have died without admission to hospital". Many reports (British Medical Journal, 1964; Matthew and Lawson, 1966; Rasmussen, 1966; Matthew, 1968; Matthew et al., 1968; Matthew et al., 1969; Burston, 1969; Kennedy et al., 1969, Freeman et al., 1969), have been published describing the clinical signs and symptoms and management of cases of acute drug poisoning. Observations on the psychiatric aspects of these patients have been reported by Kessel (1965), Kessel and McCulloch (1966), McCulloch and Philip (1967), McCulloch et al., (1967), Aitken and Carstairs (1968), and Kreitman et al., (1969). Little work, however, has been done on the effects of overdose of drugs on brain functioning during acute drug poisoning and subsequent recovery.

IV.C.

REVIEW OF THE LITERATURE:

Isolated EEG studies of coma patients were recorded in the early literature, e.g. by Berger (1932), Gibbs et al., (1937)/

(1937) were the first to comment that marked slowing was characteristic of a variety of comatose states. Davis and Davis (1939) believed that the delta activity in coma was analogous to the delta of deep sleep, an opinion with which Strauss et al., (1952) later concurred. In study of delirium Romano and Engel (1944) observed a general correlation between degree of disturbance of consciousness and the degree and character of the EEG slowing, regardless of the aetiology of the comatose state. However, exceptions to the rule of delta slowing in coma were reported by Fischgold and Bounes (1946), Loeb and Poggio (1953), Gastaut (1954), Whelan et al., (1955), Lundervold et al., (1956) and Kaada et al., (1961). In line with the investigation of Bancaud et al., (1955) and of Dell (1957) on cerebral lesions with and without disturbances of consciousness, Mathis et al., (1957) proposed that reactivity in comatose states was an important prognostic sign. Lennox and Petersen (1958) found a good correlation between clinical severity and EEG changes in patients with carbon monoxide poisoning. Pampiglione (1962) reported on 20 children with cardiac arrest and considered subsequent early EEGs to be of prognostic value. Loeb (1958) failed to find the EEG a reliable index of coma depth. He also described a variety of EEG patterns in 25 selected coma patients with verified brain lesions and concluded that generalized slowing was not to be found in this type of coma and that there was no definite relationship between the degree of coma and/

and the types of EEG change.

The most exhaustive study of coma was reported by Fischgold and Mathis (1959). They studied 155 patients, roughly one-third of whom had coma due to trauma and one third due to space-occupying lesions; only three cases were of toxic or metabolic origin. They described four stages of coma from both the clinical and the electrical viewpoints. On their scheme the EEG in Stage I shows a mixture of alpha, theta and some monophasic frontal or focal delta activity and with alerting stimuli usually cause some initial blocking - patients can be aroused and when alerted have no loss of cephalic reflexes. In Stage II, only motor or monosyllabic verbal responses to stimuli can be obtained; the EEG shows delta activity which alternates with flattened and faster rhythms during periods of cardiac and respiratory slowing; alerting stimuli rarely cause blocking, but more often accentuate the delta activity (at times some alpha and theta may appear or a delta focus become apparent). In Stage III all contact is lost, all cephalic reflexes disappear, vegetative derangements ensue and at times a state of decerebrate rigidity exists; the EEG tends to become flat and is rarely affected by any arousal stimuli. In Stage IV life has to be supported by artificial respiration. The EEG in this stage is isoelectric. The prognosis, they reported, is progressively graver as one proceeds down the scale of coma - from 25% mortality in Stage I to 100% in Stage IV. As far as differentiating coma from other states, they concluded that there were no electrical properties specific for coma and "still less for a determined aetiology".

Jouvet (1959) described Stage IV isoelectric comas
of/

of traumatic origin in 4 patients who were trephined; he found electrical silence in the thalamus as well as in the scalp recording. He felt that efforts to maintain life with artificial respiration for more than 24 hours were hopeless if the EEG remained isoelectric, a sentiment with which Schwab et al., (1962) concurred. On the other hand, Bental and Leibowitz (1961) published a case of possible encephalitis in which the EEG was flat for weeks, yet the patient ultimately recovered. Loeb (1959) emphasised that considerable care must be exercised in assessing a flat record in a coma patient; with stimulation (e.g. mechanical opening and closing of eyelids) some reactivity and a normal appearing alpha rhythm may be demonstrated, particularly when the lesion is in the upper two-thirds of the pons. Chatrian et al., (1963) observed normal sleep state potentials in some cases of trauma in which there may have been depression of the reticular activating system with consequent coma.

Silverman (1963) in a retrospective study reviewed the EEG of 184 patients in relation to coma depth and the EEG. He divided clinical and electrical findings into four stages of coma identical with those of Fischgold and Mathis (1959). Seven out of twelve cases of drug intoxication were Stage I, one Stage II and four Stage III. He concluded that study of the electrical responses to external stimuli, as well as the appearance of sleep state potentials, gave a reasonable electrical indication of coma depth. In Stage I, coma reactivity and sleep approached the normal; in Stage II both/

both reactivity and sleep became distorted; in Stages III to IV both reactivity and sleep disappeared and the record tended to become monorhythmic and finally isoelectric. It was further concluded that a marked discrepancy between the clinical and electrical signs of deep coma suggests a brain stem lesion with a relatively intact cortex. He added that the finding of a barbiturate fast type of EEG record or of the mixed fast-theta records was suggestive of barbiturate or other sedative drug poisoning.

An isoelectric EEG in a patient with deep coma has become a problem in recent years with the greater success of resuscitation teams and with the greater efficiency in maintaining circulation and respiration in intensive care units. As surgeons and immunologists have made advances in organ transplantation, patients in irreversible coma become the main source of donor organs. Obviously the patient must be certifiably dead before organs can be transplanted, yet the organs must not have undergone degeneration. This has raised questions regarding the truth and certifiability of death and the exact time of death. With respect to the latter, there are two alternatives, either to await the cessation of the heart after the withdrawal of mechanical aids, or to declare the patient dead before such withdrawal once the irreversibility of the coma is established. Exceptions to the rule of cerebral death with isoelectric EEGs have been reported in the literature. It has been shown (Dpitz and Schneider, 1950) that in animals during experimentally produced anoxia the EEG becomes progressively lower in amplitude until it reaches zero potential, and if this anoxic state is allowed to persist for more than approximately four/

four minutes, the brain and the EEG will not recover their function (Schneider, 1961 a,b.), and in dogs Spoerel (1962) found a time of from 3 to 5 minutes from onset of ischaemia to irreversible EEG electrical silence. Under experimental conditions normal cardiac and respiratory function is usually maintained, so that perfusion of the brain with normally oxygenated blood follows immediately on cessation of anoxia; these conditions do not usually occur in clinical situations.

The changes observed in the human EEG during anoxia have been described by many investigators. Gronquist et al., (1952), Bellville and Howland (1957) and Brechner et al., (1961) have described fast (16-25 cps) low voltage activity ("file pattern") in otherwise severely depressed or flat records. Bellville et al., (1955) noted slowing within 4 seconds of cerebral ischaemia in a patient undergoing cardiac surgery. Thies-Puppel and Wieners (1961) studied 30 patients undergoing cardiac surgery during hypothermia, and found that the interval between onset of ischaemia and disappearance of all electrical activity of the brain varied from 12-60 seconds. Return of EEG occurred between 30 seconds to 4 minutes after restoration of blood flow when ischaemia had been less than 7 minutes and up to 25 minutes after over 8 minutes of ischaemia. Brechner et al., (1961) noted that the EEG reappeared and became normal within minutes after cardiac arrest of only 2 minutes.

Bickford and co-workers (1965) reported their experience with twenty five post-anoxic patients initially comatose. The irrecoverable state /

state exhibited a flat EEG with no reactivity. In partly recoverable states EEG activity ranged from burst-suppression patterns to diffuse delta, while in the reversible cases, patterns ranged from diffuse delta to non-responding spindle formation activity.

Hookaday et al., (1965) reported EEG changes in 39 comatose patients who had suffered cardiac arrest (26) or who had apnoea (13).

The EEGs were classified into 5 grades, each with two subdivisions (a, b).

GRADE I (Within normal limits)

- a. Alpha rhythm.
- b. Predominant alpha with rare theta.

GRADE II (Mildly abnormal)

- a. Predominant theta, with rare alpha
- b. Predominant theta, with some delta.

GRADE III (Moderately abnormal)

- a. Delta, mixed with theta and rare alpha.
- b. Predominant delta, with no other activity.

GRADE IV (Severely abnormal)

- a. Diffuse delta, with brief isoelectric intervals.
- b. Scattered delta in some leads only with absence of activity in other leads.

GRADE V (Extremely abnormal)

- a. A nearly flat record.
- b. No EEG at all.

This system of classification consisting of ten types of EEG abnormality (5 grades each with two subdivisions) was, therefore, used in a selected group of patients of acute cerebral/



cerebral anoxia. The anoxia was in every case sufficiently severe so that early recovery of consciousness failed to occur and the emergency EEG was obtained to establish whether the brain was alive and, if so, whether clinical recovery would follow.

Only 6 of the 39 patients survived. Patients with records of Grades IV and V (26) had a nearly hopeless prognosis as only one (Grade IV) survived. Patients with EEGs of Grade I, who invariably were conscious at the time of recording, carried an excellent prognosis for full recovery. Records of Grades II and III were of less certain prognostic value as only one of three of Grade II and three of nine survived. Their overall accuracy of prognosis was 83%. They concluded that the EEG can be of considerable help in establishing death in the presence of a restored heart beat, and suggested that further attention be given to the definition of death.

It has also been known experimentally and clinically that anaesthetics produce periods of isoelectric activity in the EEG. Kiersey et al., (1951) studied the EEG patterns after thiopentone sodium anaesthesia to patients undergoing surgical treatment for varicose veins of the legs. They analysed the frequencies with the Grey Walter frequency analyser, and classified the EEG changes into five patterns. The first pattern (fast) was characterized by high-amplitude, fast, spiky activity of mixed frequencies varying between 10 and 30 cps with the predominant frequency near 20 cps. During this pattern, consciousness, though dulled, was retained in the early phases. The second pattern (complex) consisted of many frequencies of predominantly slower/

slower wave forms of very irregular contour and random occurrence. Superimposed on these slower waves and occupying the intervals between them was a faster activity at about 10 cps rather spiky in character and irregular in amplitude. This second pattern was accompanied by loss of consciousness and reduced reflex activity. Withdrawal reaction to painful stimuli was abolished. The third pattern was characterized by a progressive suppression of cortical activity taking the form of short periods of relative quiescence that separate groups or bursts of waves. In this pattern the periods of inactivity did not exceed three seconds in length. As the third pattern appeared, reduction of respiratory minute volume became more marked. The fourth pattern differed from the third in respect of duration of the periods of cortical inactivity which were defined as lasting between three and ten seconds. The amplitude of the waves in the periods of activity was slightly less than in the third pattern but the frequency characteristics remained unaltered. In the fifth pattern periods of inactivity did not appear more frequently than once every ten seconds and there was further reduction in the amplitude of the component's to below 25 microvolts. The frequency of the waves was the same as that found in the active phases of the fourth pattern. There was marked respiratory depression, possibly requiring a respirator. The pupils retained some reaction to light.

Several reports have discussed the EEG changes in man during hypothermia. Pearcy and Virtue (1959) described EEG changes in 74 patients subjected to hypothermia. Beginning temperatures were 36.0 to 37.0°C and changes were determined at the lowest temperature reached. Twenty nine patients showed no change as/

as cooling progressed, thirty nine patients showed a tendency toward slowing of frequency, even though this was usually slight. A typical change was a reduction from 16-17 cps at 36.0°C to 13-14 cps at 30.0°C . Of five records of patients whose temperature fell below 29.0°C , four showed decrease in frequency. In two voltage increased, in two others no change in voltage appeared. The one record showing increased frequency also showed a decreased voltage. None of their patients had complete cessation of cerebral electrical activity. Hale and Moraca (1958) reported slowing of frequency and decrease in voltage in the EEG with cooling by infusion of cold blood from a pump oxygenator. Scott (1955) reported 25 patients cooled to 28.0°C for resection of berry aneurysms. With decrease in temperature there was a reduction in voltage from 60-80 microvolts to 50 microvolts. Below 30.0°C the voltage drop continued and the record became irregular but without suppression.

More extensive work has been reported in animals. Callaghan et al., (1954) reported progressive flattening of the EEG of monkeys as the temperature was lowered. At 20.0°C there was minimal activity present. During rewarming the rhythms returned in reverse order. McMurrey et al., (1956) described changes seen in the EEG of monkeys subjected to hypothermia and cerebral occlusion. They observed flattening of the EEG after one minute of total occlusion, and noted recovery time was directly related to occlusion time. Gaenshirt et al., (1954) cooled isolated cat's heads by perfusing with cooled blood from/

from a donor cat, and found a slowing of frequency with an increase in voltage to 30.0°C , below 30.0°C dysrhythmia appeared with slow frequencies dominating and the voltage decreased. Their records became isoelectric between 15.0°C and 20.0°C .

Techniques such as spectral analysis and autocorrelation have also been used in studying EEGs in coma. Ferillo et al., (1969) have made a spectral analysis of the EEG activity of patients in comatose states arising from organic brain lesions and were able to record oscillatory periodic potentials ("rhythmic" activity) in all degrees of coma except in the terminal stage of coma or coma "depasse". The dominant rhythmic activity belonged to the delta band. Theta and alpha rhythms could be recorded. They concluded that a certain organisation of the cerebral electrical activity is compatible with a severe disorganisation of cerebral functioning. However they did not find any clear-cut relation of coma and type of rhythmic activity. Bergamini et al., (1965) studied the EEG rhythm of six subjects in post-traumatic coma and suggested aperiodic coma delta rhythm was probably a sum of electrical potentials which were only apparently rhythmical but which in reality represented a bioelectrical activity without periodic events, of random type.

The investigations reported so far are based on either retrospective studies or EEG recordings for a short time. The reports on EEG changes, particularly regarding the significance of flat records in cases of coma, are conflicting (Jouvet, 1959; Loeb/

Loeb, 1958; Bental and Leibowitz, 1961) possibly because in all these studies EEG recordings were done only for short periods. The existing literature does not contain any report of continuous EEG recording of comatose patients from the time of admission to hospital till their recovery from coma. It appeared likely to me, that continuous EEG recording or EEG recording over fairly long periods might be important for the understanding of the significance of the various EEG changes seen in coma.

The published reports (Fischgold and Mathis, 1959; Chatrian et al., 1963) reveal a lack of correlation between the clinical and electrical signs of depth of coma. Moreover most studies have been done on patients with organic brain disease, including head injury, and little is known about drug-induced coma.

Many pharmacological agents influence the EEG but because of the widespread use of barbiturates for sedation, anaesthesia, and in the therapy of convulsive disorders, the EEG effects of this drug group have been studied more widely than others. Earlier reports emphasised the similarity between records obtained under barbiturate sedation and those of natural sleep (Berger, 1931; Lennox et al., 1936, Gibbs et al., 1937). There has been increasing emphasis on the initial appearance of fast activity preceding the loss of consciousness (Cohn and Katzenelbogen, 1942; Brazier and Pinesinger, 1945; Brazier, 1948). In very heavy doses, as in deep anaesthesia near the collapse stage (Brazier, 1951) silent periods are interrupted by bursts of activity (Swank and Foley, 1948; Lous et al., 1949; Kiersey et al., 1951) or "suppression-burst activity".

Wulff/

Wulff (1950) studied 26 patients suffering from acute barbiturate poisoning. EEG records were taken daily until the patient either recovered consciousness or died. In one case cortical activity was absent. In the most severely poisoned patients, periods of absent cortical activity (blackouts) of a few seconds to several minutes duration were observed. Most of these cases died, but the blackouts disappeared before death. Neither variations in blood pressure (from subnormal to normal) nor oxygen therapy had any effect on the blackouts. He suggested that presence of blackouts indicated an unfavourable prognosis.

Mantz and his co-workers (1965) reported six cases of severe barbiturate coma with episodes of five to one hundred and eighty seconds of EEG flattening interrupted by paroxysmal, high voltage bursts. All the six cases recovered, and the authors emphasised that a well-conducted reanimation programme "can succeed in intoxications classically considered mortal". Bird and Plum (1968) reported a case of acute barbiturate poisoning who had an isoelectric EEG record for twenty-three hours but recovered after five days of coma.

Sament and Huott (1969) from the Massachusetts General Hospital have reported EEG changes in 26 cases of acute barbiturate poisoning. Seven of twenty six (27%) cases died, including every one of their six cases which had completely isoelectric records (Stage VI). The remaining death was in a patient who had an isoelectric record with bursts of sharp activity (Stage V). Their stages I-III were associated with drowsiness or confusion and Stages IV-VI with coma. These authors/

could not distinguish clinically the three stages (IV-VI) associated with coma but found a correlation between these EEG changes and complications. Cardiac arrest occurred only during Stage VI, whereas respiratory failure occurred during Stages III-VI, and the authors emphasised "if these complications can be prevented, all cases of barbiturate intoxication are potentially reversible".

The majority of the reports published so far have been concerned with EEG changes in acute barbiturate intoxication. There is only one single case report, by Wallace and Allen (1968) of EEG changes in "Mandrax" overdose. They found a "flat" EEG with irregular bilateral spike complexes appearing at intervals of 1-8 seconds. The patient recovered and 13 days after the drug her EEG was reported to be "nearing normal".

The care of a patient who has taken an overdose of a psychotropic drug must be based on the clinical assessment of the patient, with the assistance of a toxicologist. However, if we are to advance our understanding of coma we must be able to follow the behaviour of the important physiological variables continuously. A record of these changes may make it possible to compare cases and establish significant points of change during the coma. These could be correlated with the toxicological findings.

The existing literature shows that EEG studies have been entirely based on sampling, using short runs of EEGs usually without consideration of any other variables. Some attempts have been/

been made to correlate the degree of abnormality of EEG and the clinical level of consciousness. As far as long term EEG monitoring is concerned, this has been almost exclusively used in sleep research and then rarely carried on for more than 10-12 hours at a time.

IV.D.PATIENTS AND METHODS:-

The investigation was carried out at the Edinburgh Regional Poisoning Treatment Centre which serves a population of about half a million in Edinburgh and the surrounding district. All adult cases of acute drug poisoning are admitted, regardless of the severity of the poisoning. The number of admissions has doubled in the past five years and in 1968 there were 1067 admissions (634 women and 433 men). The unit has seven-day laboratory support for the qualitative and quantitative estimation of commonly involved poisons. The functioning of the unit has been described in detail by Matthew et al., (1969).

On admission each patient was examined by one of the ward physicians to assess the clinical level of consciousness and was graded into one of the following grades (Matthew and Lawson, 1966).

- * Grade 0 - Fully conscious.
- Grade 1 - Drowsy but responds to verbal commands.
- Grade 2 - Response to mild painful stimulation.
- Grade 3 - Minimum response to maximum painful stimulation.
- Grade 4 - No response to maximum painful stimulation.

-
- * The clinical grade of coma is not to be confused with the EEG grading. To enable easy distinction, the clinical grade will be designated by Arabic numerals and the EEG grade by Roman numerals.

Rubbing the patient's sternum with the knuckles was used as the standard painful stimulus.

The level of consciousness and progress of the patient while under care was based on repeated clinical evaluation and regular sampling of such physiological variables as temperature, pulse rate, blood pressure and respiration. This was supported by supplementary investigations where possible, such as estimation of the blood levels of the toxic drug, assessment of serum electrolyte levels and blood gases. The clinical examination included assessment of the presence of any co-existing disease which would have made the patient more vulnerable to the toxic effects of the drug.

Continuous EEG monitoring was started as soon as possible after admission to the ward. A delay of two to three hours between admission of the patient and starting the EEG recording was quite common owing to the fact that some patients required such procedures as intubation, stomach washout or special nursing procedures before preparation for EEG recording.

IV.E.

PREPARATION FOR RECORDING USED IN PROJECT 2:-

Silver cup electrodes were filled with electrode jelly and were attached to the scalp with the collodion, in positions F_2 , C_2 , P_2 , F_4 , C_4 , P_4 , F_3 , C_3 , and P_3 , of the international "10/20" system of electrode placement. Every attempt was made to attach the electrodes in the desired position despite awkward/

awkward positions of the head in some unconscious patients. It was particularly difficult to fix the electrodes when the foot of the bed was raised to support the blood pressure or when the patient was attached to a ventilator.

A central montage with the following channels was used in most of the patients studied.

Channel 1	-	$F_Z - C_Z$
2	-	$C_Z - P_Z$
3	-	$F_Z - F_4$
4	-	$F_Z - F_3$
5	-	$C_Z - C_4$
6	-	$C_Z - C_3$
7	-	$P_Z - P_4$
8	-	$P_Z - P_3$

This central montage proved to be advantageous as this allowed the patient's head to be kept on the side, an important principle in the management of unconscious patients.

In some cases two extra electrodes, one on the left 3rd or 4th intercostal space, 1" from the midsternal line and the other on the left shoulder, were attached to monitor the ECG. It was found possible though not easy to continue ECG recording whilst the patient was receiving active nursing attention.

Each electrode had 4 inches of wire and was connected to the headbox by means of a longer connecting lead. (Fig. 13b). This procedure made it possible to disconnect the patient from the machine for nursing care, physiotherapy, or when the patient became/

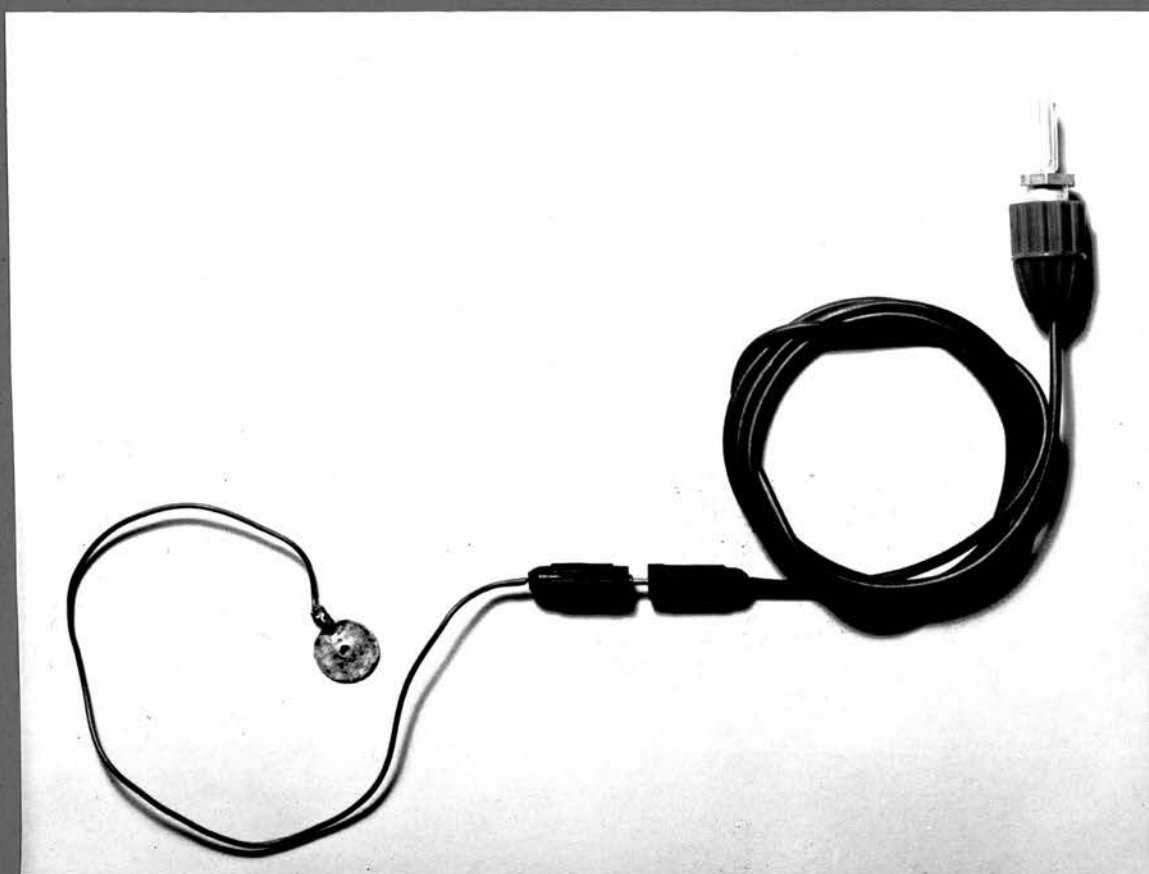


Fig. 13 B.

Each silver disc electrode with 4 inches of wire (left) was connected to the head box by means of a longer connecting lead (right). This procedure made it possible to disconnect the patient from the EEG machine when necessary.

restless at about the time of regaining consciousness. The resistances of the electrodes were checked to ensure that they were below 10 K ohms.

The EEG machine used in this project was a portable 16 channel Elema-Schonander Mingograph. It is specially modified for continuous recording and is capable of running from batteries as well as from the mains supply. Therefore, it was possible to move the machine to the bed-side of the patient. The machine was run at a constant speed of 1.5 cm. per second, producing 4000 sheets of recorded paper over the 24 hour period.

As a routine procedure the machine was calibrated at 1 cm. per 100 microvolts ($\mu\text{v.}$) time constant = 0.3 second and high frequency filters = 0. Precautions were taken to ensure an artefact-free record.

In each patient recordings were made continuously throughout the period of unconsciousness till either the patient recovered or died. After recovery twice daily recordings were usually made and a pre-discharge full-montage EEG.

When patients were medically fit to be discharged from the hospital, a battery of psychological tests were administered to the first forty patients in the hope of detecting any possible organic brain damage. The battery was made up of the following tests:-

- I. The Mill Hill Vocabulary Scale (Synonym only) Form 1 Senior. (Raven, 1958 a.)
- II. The synonym Learning Test. (Kendrick, 1965).
- III. The Digit Copying Test. (Kendrick, 1965).
- IV. Raven's/

- IV. Raven's Progressive Matrices.
- V. Design Copying Test. (Orme et al., 1964)

At intervals of one, three and nine months, after discharge from hospital the first forty patients attended for follow-up examination, when both EEG and psychometric tests were repeated; while in a further thirty nine cases only EEG examination was repeated. As no evidence of residual brain damage was found in these patients the follow-up procedure was discontinued.

IV.F.

ANALYSIS OF THE RECORD:-

All records from each patients were read page by page by the author. This involved the analysis of approximately two thousand hours of EEG record, or roughly 83 miles of paper. As no internationally agreed method of scoring coma records comparable to that for analysing sleep records is available, a system of classifying these records had to be established. After recording the first few records the following system of classification was found useful and these criteria were employed in scoring all the records.

An EEG was classified as follows:-

- *
GRADE I - When it contained alpha rhythm or predominant alpha with beta or some rare theta; this type of abnormality is illustrated in Fig. 14, taken from a case of nitrazepam overdose 16 hours after ingestion of 40 tablets (200 mg.) of nitrazepam. It shows drug-induced 16-18 cps.

* Note that Roman numerals are used for the EEG grade of coma.

EXAMPLE OF EEG ABNORMALITY IN ACUTE DRUG POISONING.

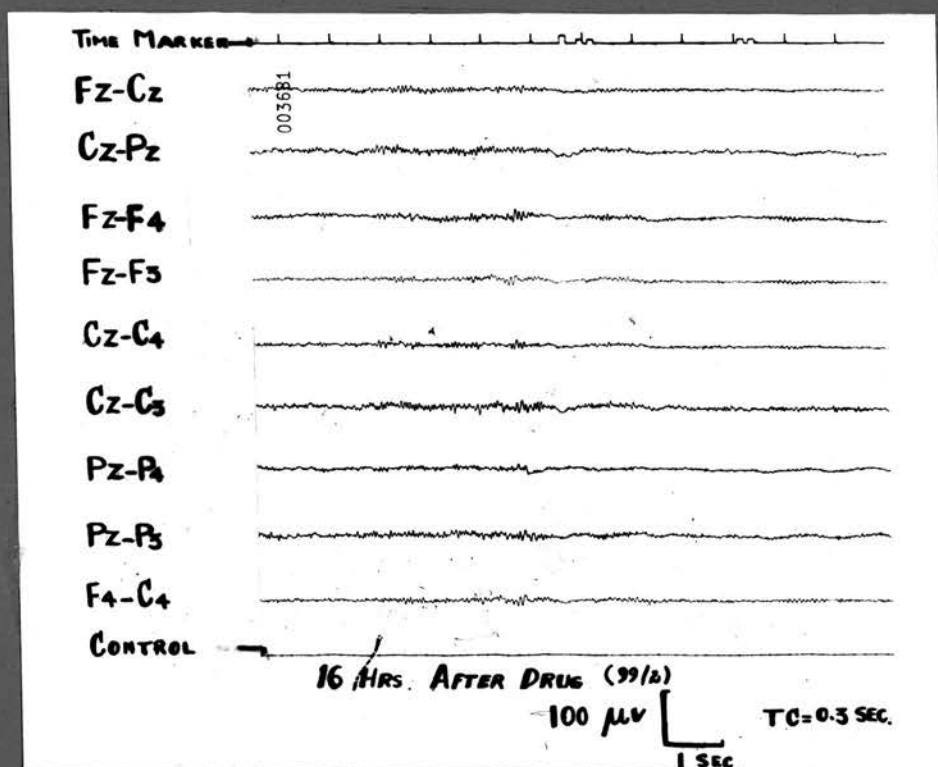


Figure 14:

Grade 1 EEG abnormality. Drug-induced 16-18 cps activity, after nitrazepam overdose. Patient 82, female, 19 years old.

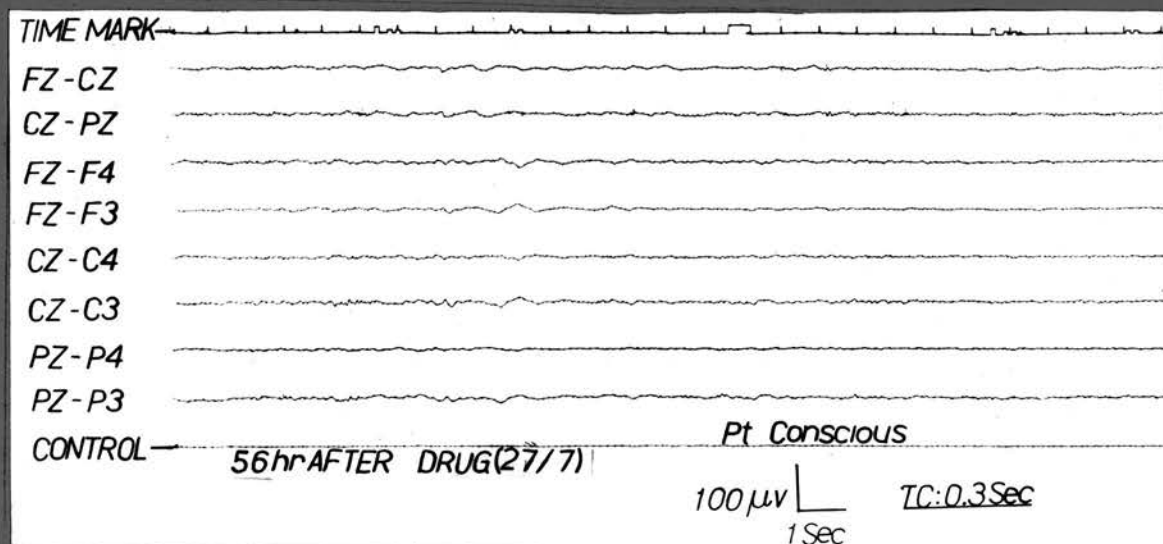


Figure 15:

Grade II EEG abnormality. Dominant activity at 5-8 cps with bursts of slow wave activity at 1-4 cps, in a case of phenobarbitone overdose. Patient 5, Male, 56 years old.

- GRADE II - Where there was predominant theta with some alpha, beta and low voltage delta as illustrated in Fig. 15 from a phenobarbitone overdose 56 hours after ingestion of the drug.
- GRADE III - When it showed the presence of predominant low/high voltage delta mixed with some theta. This is illustrated in Fig. 16 from a case of meprobamate overdose 20 hours after drug ingestion.
- GRADE IV - When it contained delta with or without brief isoelectric intervals, as illustrated in Fig. 17 from a case of phenobarbitone poisoning, 30 hours after drug ingestion.
- GRADE V - When it contained suppression-burst activity (Fig. 18) namely where 5-10 cps activity of several seconds duration would alternate with electrical silence.
- GRADE VI - When it contained near silence (Fig. 19) but with isolated and low voltage 3-7 cps waves occurring singly or bursts of half a second.
- GRADE VII - An isoelectric record totally unresponsive to any stimuli. (Fig. 20 a. and 20 b.)

IV.G.

STATISTICAL METHODS:-

In this project a rank correlation method was used. In view of the nature of the data the most suitable technique was that developed by Kendall (1955). This is the correlation statistic "tau". The technique used for calculating tau involved contingency tables and hence there were a great many tied ranks. The value of tau obtained had therefore to be corrected for continuity thereby giving a unit normal deviate (z). The significance of this z was evaluated in the usual way giving exact probability values. For example z values of 1.64 and 2.33 give a significance level of $p = 0.05$ and $p = 0.01$ respectively.

It/

EXAMPLES OF EEG ABNORMALITY IN ACUTE DRUG POISONING.

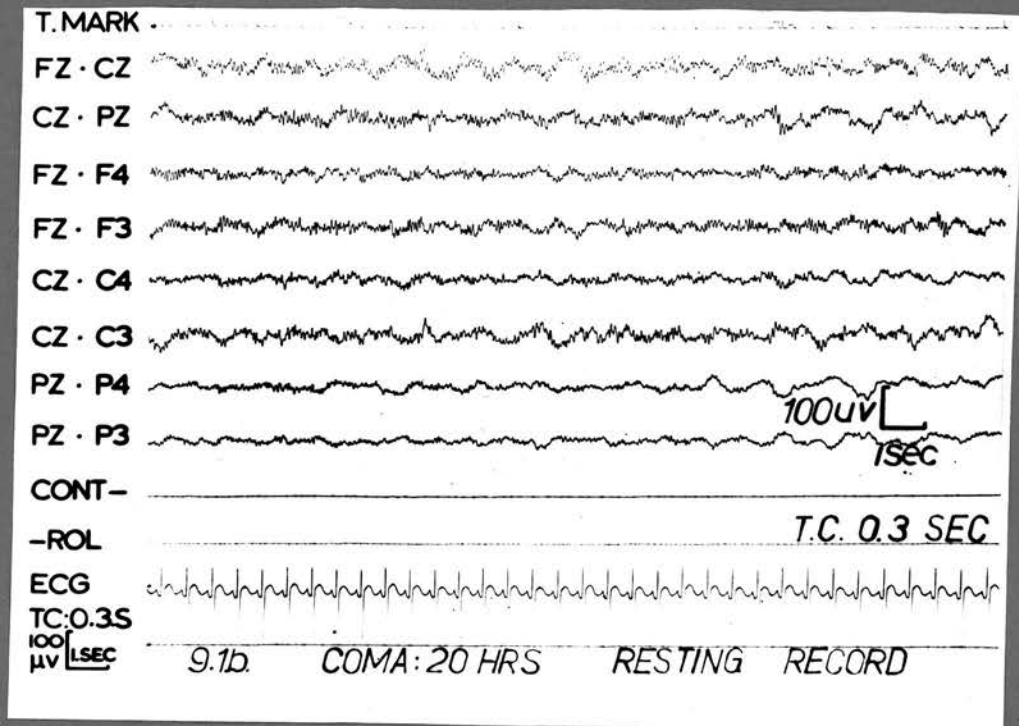


Figure 16:

Grade III EEG abnormality in a case of meprobamate poisoning. Dominant activity at 1-2 cps with some 3-5 cps activity on which was superimposed fast activity of 14-18 cps. Patient 118, Female, 20 years old.

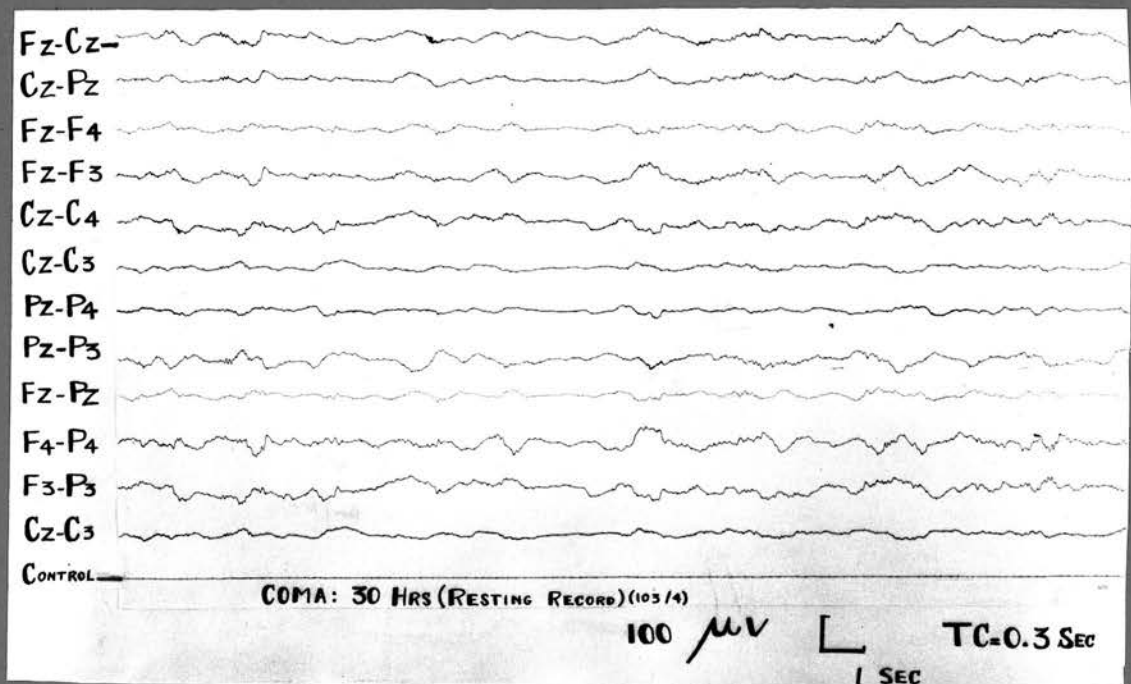


Figure 17:

Grade IV EEG abnormality. Almost continuous slow wave activity at $\frac{1}{2}$ -1 cps, after phenobarbitone overdose. Patient 11, Female, 28 years old.

EXAMPLES OF EEG ABNORMALITY IN ACUTE
DRUG POISONING.

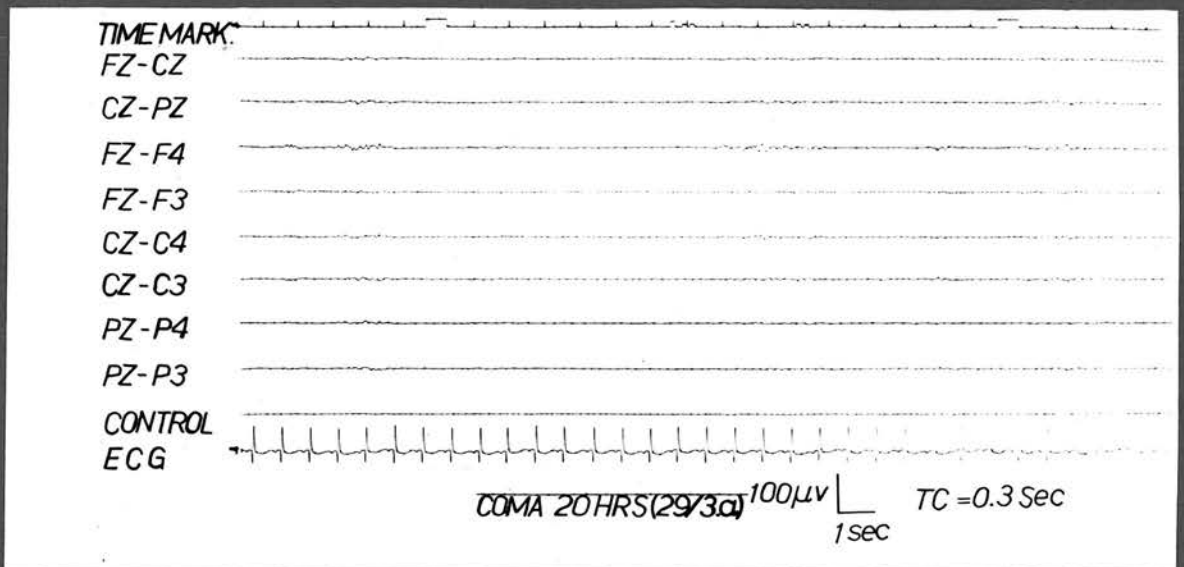


Figure 18:

Grade V EEG abnormality (suppression burst activity), 5-10 cps activity of several seconds duration alternates with electrical silence, in a case of barbitone overdose. Patient 14, Female, 64 year old.

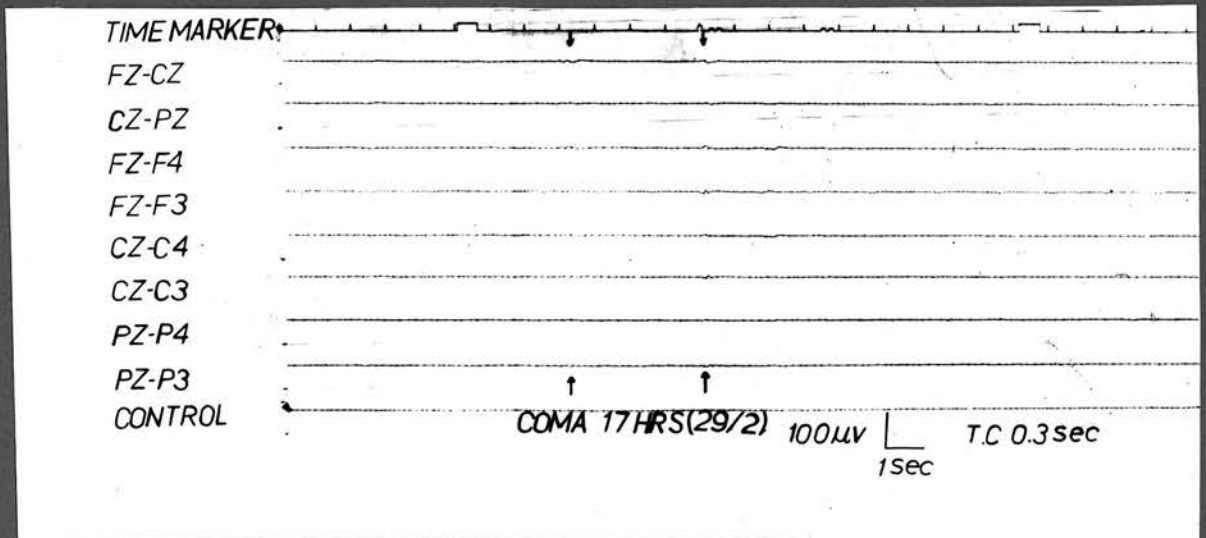


Figure 19:

Grade VI EEG abnormality. Low voltage 3-7 cps waves occurring singly (marked with arrows), after ingestion of barbitone. Patient 14, Female, 64 year old.

EXAMPLES OF EEG ABNORMALITY IN ACUTE DRUG POISONING.

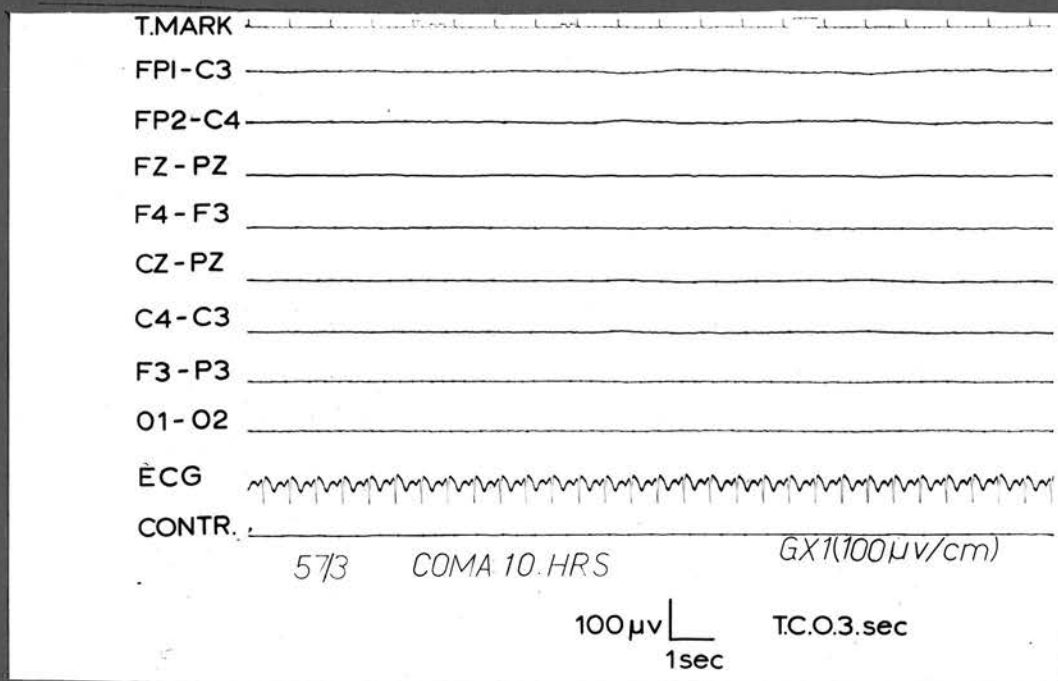


Figure 20 a.

Grade VII EEG abnormality; an isoelectric record at average gain (100 μv/cm), in a case of orphenadrine and promazine poisoning. Patient 104, Male, 41 years old.

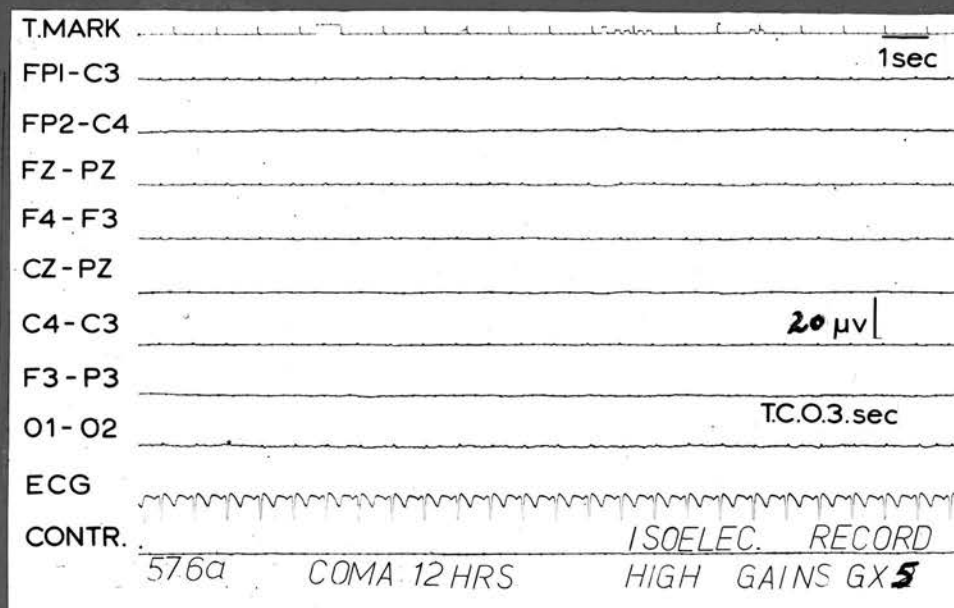


Figure 20 b.

Grade VII EEG abnormality. Same patient's record at maximum amplification (20 μv/cm) contained ECG artefacts at increased sensitivity but remained isoelectric.

It is appreciated that there are probably correlations between all the parameters although only the correlations with the EEG gradings have been quoted. These additional correlations would imply that partial correlation should be calculated. However rank correlation methods do not lend themselves easily to this form of correlation.

IV.H. PATIENTS:-

One hundred and twenty seven patients formed the population studied. All were in-patients of the Regional Poisoning Treatment Centre, Edinburgh, between January 1968 and July, 1969. All patients were admitted because of acute drug poisoning. Patients with a history of carbon monoxide poisoning alone or in conjunction with other drugs were excluded. The total number of male and female patients together with the drug ingested are shown in Table 22. All patients except 4 made clinical recovery from acute drug poisoning. The main drugs involved were barbiturates, Mandrax (a combination of methaqualone 250 mg. and diphenhydramine hydrochloride 25 mg.) and nitrazepam. As barbiturates alone accounted for approximately half the patients this drug group has been discussed separately, the other drugs having been combined for the presentation of the results.

All the 23 patients in the Mandrax group survived. One patient, however, (see case histories - Case No.4) though recovering from the acute drug poisoning, on the 7th day after admission/

NUMBER OF MALE AND FEMALE PATIENTS AND
DRUG INGESTED BY - 127 PATIENTS.

DRUG GROUP	MALE	FEMALE	TOTAL
BARBITURATES	15	35	50
MANDRAX	9	14	23
NITRAZEPAM	2	17	19
TRICYCLIC COMPOUNDS	3	7	10
OTHERS	6	19	25
TOTAL	35	92	127

TABLE 22

developed ventricular fibrillation and died. As can be seen from his history there was considerable prior pathology. Another patient (Case No. 61) developed two transient cardiac arrests from which she was resuscitated, while another patient (Case No. 54) required assisted ventilation 13 hours after admission and was kept on a Bird respirator for 14 hours. Five cases showed some ECG abnormality. A small amount of alcohol in addition to 18 tablets of Mandrax was ingested by one patient (Case No. 62) though the blood concentration of alcohol was not estimated.

Ten patients were studied who had been admitted for overdose of tricyclic compounds (Table 22). This group was composed of 5 who had taken amitriptyline, 3 imipramine, one nortriptyline and one protriptyline. One patient (Case No. 101) had taken an uncertain amount of alcohol in addition to imipramine. Four patients (Cases Nos. 93, 94, 95 and 98) developed some cardiac irregularities but in none was the irregularity serious and all disappeared as they recovered. Three patients (Cases Nos. 93, 94 and 98) developed fits. All patients survived.

Nineteen cases of nitrazepam poisoning were included (Table 22). All made a full clinical recovery, from acute drug poisoning. Three patients (Cases Nos. 79, 83 and 91) had taken some alcohol in addition to nitrazepam but the blood alcohol concentrations were not estimated.

It will be noticed that for the nitrazepam group
of/

of patients correlations between EEG grades and other parameters are not presented. This is because all the 19 patients were either EEG grade I or II. Any correlation found therefore would be meaningless owing to the clustering of the patients in these two EEG grades.

The miscellaneous (other) group was made up of 6 men and 19 women. The drugs involved are shown in Table 23. Three patients died (Cases Nos. 104, 108 and 126). The first (Case No. 104) had taken orphenadrine hydrochloride (Disipal) in combination with promazine (Sparine) and, on admission to the ward, developed cardiac arrest for approximately 5-7 minutes from which he was resuscitated but died 16 hours after admission. The second patient (Case No. 108) was admitted to the ward in an unconscious state. A blood examination revealed only a small amount of barbiturate (1.2 mg.%). He developed cardiac arrhythmias and died 20 hours after admission. The third patient, a young female (Case No. 126) had taken paracetamol and ferrous sulphate tablets and collapsed. After admission to the ward she had severe gastro-intestinal haemorrhage and died.

One patient (Case No. 110) who took Diconal * and Mandrax made a clinical recovery from acute drug poisoning but suffered brain damage, manifesting itself as a persisting dementia with disorientation and recent memory impairment. One patient (Case No. 120) had taken a small amount of alcohol with the tablets but blood alcohol concentration was not estimated.

* Diconal is a combination of dipipanone hydrochloride 10 mg. and cyclizine hydrochloride 30 mg.

NUMBER OF PATIENTS AND DRUG INGESTED BY
25 CASES OF MISCELLANEOUS (OTHER) GROUP.

<u>DRUG OR DRUGS</u>	<u>NUMBER OF PATIENTS</u>
MEPROBAMATE	3
GLUTETHIMIDE + BARBITURATES	1
GLUTETHIMIDE + DIAZEPAM	1
GLUTETHIMIDE + NITRAZEPAM	1
DICHLORALPHENAZONE	1
QUINALBARBITONE + TRIFLUOPERAZINE + NITRAZEPAM	1
BARBITURATES + ?	1
BARBITURATES + SALICYLATES	2
CARBRITAL	1
ETHCHLORVYNOL	1
METHYPRYLON	1
ORPHENADRINE + PROMAZINE	1
MANDRAX + DIPIPANONE HYDROCHLORIDE	1
BARBITURATES + ANTIDEPRESSANT + ALCOHOL	1
BARBITURATES + PHENOTHIAZINE	1
FENFLURAMINE	3
THYROXINE	1
SALICYLATE + ?	1
PERPHENAZINE + ?	1
PARACETAMOL + FERROUS SULPHATE	1
	<hr/>
Total	<u>25</u>

TABLE 23

IV.I.EEG ABNORMALITY IN THE INITIAL RECORD:-

Each patient's record was classified in terms of the EEG grade as described previously. The EEG abnormality, as seen in the initial record of the patients in the various drug groups, is shown in Table 24. Forty one of the 127 cases (32%) were Grades V-VII, and of these 20 had taken barbiturate, 8 Mandrax, 3 tricyclic compounds and 10 had taken miscellaneous (other) drugs.

Forty percent of patients in both the barbiturate and miscellaneous groups, and 35% of the Mandrax group, were Grade V-VII. In the nitrazepam group, on the other hand, only minor EEG abnormalities were observed and, of the 19 cases in this group, 16 were Grade I and the remaining 3 Grade II.

In the tricyclic antidepressant group none of the 10 patients was Grade VI or VII and each revealed Grade II-V EEG abnormalities. Fifteen of the 25 patients (60%) in the miscellaneous group were Grades I-IV and all the three patients who had taken fenfluramine were Grade I.

Fifteen patients had an isoelectric record at some point during their acute drug poisoning state. In ten of these it was observed at the time of initial recording, while in the remaining five patients it was not seen till some time after admission. In two of the 4 cases of Mandrax poisoning with complete electrical silence it was seen in the initial record. In Case No. 62 it lasted for 13.50 hours and for 22 hours in/

EEG ABNORMALITY AND DRUG INGESTED BY 127 PATIENTS

DRUG GROUP	NUMBER OF CASES							TOTAL
	EEG GRADE OF COMA							
	I	II	III	IV	V	VI	VII	
BARBITURATES	-	8	8	14	8	7	5	50
MANDRAX	1	2	8	4	4	2	2	23
NITRAZEPAM	16	3	-	-	-	-	-	19
TRICYCLIC COMPOUNDS	-	2	2	3	3	-	-	10
OTHERS	3	2	6	4	4	3	3	25
TOTAL	20	17	24	25	19	12	10	127

TABLE 24.

in case No. 59. Three patients (Cases 104, 108 and 126) from the miscellaneous group had a flat record at the time of initial recording and, as can be seen from the case histories, all three died.

IV.J.

AGE GROUP:

The age distribution of all the 127 patients is presented in Table 25. Fifty two percent of the barbiturate group, 60.8% of Mandrax poisoning, 50% in the tricyclic antidepressant group and 36% of the miscellaneous group were above the age of 40.

Twelve percent of the patients of the barbiturate group, 9% of the Mandrax group, 10% of the tricyclic compound group and 8% of the miscellaneous group were above the age of 60 years. The correlation between age and EEG grade of coma (Table 26) for the various drug groups was found to be significant ($p = 0.05$) for the Mandrax and the tricyclic group. However, the overall correlation between age and EEG depth of coma was not found to be significant ($z = 1.38$, $p = 0.08$).

IV.K.

CLINICAL ASSESSMENT OF DEPTH OF COMA:-

The clinical depth of coma in relation to the drug ingested by the 127 patients is shown in Table 27. Twenty two patients (17%) were conscious on admission and these included all/

AGE IN YEARS OF PATIENTS AND DRUG INGESTED

DRUG	AGE IN YEARS	NUMBER OF CASES					TOTAL
		19	20/39	40/59	60/79	80 +	
BARBITURATES		2	22	20	5	1	50
MANDRAX		1	8	12	2	-	23
NITRAZEPAM		-	9	9	1	-	19
TRICYCLIC COMPOUNDS		1	4	4	1	-	10
OTHERS		6	10	7	2	-	25
TOTAL		10	53	52	11	1	127

TABLE 25

NON-PARAMETRIC CORRELATION BETWEEN AGE GROUP AND
EEG GRADE IN VARIOUS DRUG GROUPS.

DRUG GROUP	Tau	Correlated z	p
BARBITURATES	0.22	1.14	0.13
MANDRAX	0.40	1.68	0.05
TRICYCLIC	0.54	1.65	0.05
MISCELLANEOUS OR OTHER	0.24	1.08	0.14
ALL DRUGS *	0.21	1.38	0.08

* Note the overall correlation was calculated separately and not obtained by averaging individual correlations.

TABLE 26.

CLINICAL DEPTH OF COMA AND DRUG INGESTED

BY 127 PATIENTS.

DRUG GROUP	NUMBER OF CASES CLINICAL GRADE OF COMA					TOTAL
	0	1	2	3	4	
BARBITURATES	-	9	8	12	21	50
MANDRAX	-	3	8	8	4	23
NITRAZEPAM	19	-	-	-	-	19
TRICYCLIC COMPOUNDS	-	-	4	4	2	10
OTHERS	3	2	4	8	8	25
TOTAL	22	14	24	32	35	127

TABLE 27.

all 19 patients who had taken nitrazepam and the three who had taken fenfluramine.

Sixty seven of the 127 cases (53%) were grades 3 and 4, of whom 33 had taken barbiturates, 12 Mandrax and 6 tricyclic antidepressants. The remaining 16 cases had taken a variety of other drugs or drug mixtures.

An attempt was also made to correlate the EEG grade of coma with clinical assessment of depth of coma. EEG grade I was associated with a fully conscious patient, Grade II with drowsiness, Grades III and IV were associated with unconsciousness but the patient responded to stimulation of the sternum with the knuckles. In Grades V-VII the patient was deeply unconscious and these grades could not be distinguished clinically.

A significant positive correlation between the clinical assessment of depth of coma and the EEG grade of coma (Table 28) was found not only for all the drugs ($p = 0.002$) taken together but also separately for barbiturate ($p = 0.004$), Mandrax ($p = 0.003$), tricyclic antidepressants ($p = 0.01$) and miscellaneous drugs ($p = 0.004$).

IV.L.

TEMPERATURE ON ADMISSION:-

The patient's rectal temperature, as recorded on admission to the ward, and the drug group are shown in Table 29. Eighty five of the 127 patients (77%) had a temperature in the range 35.6°C to 37.8°C . Forty patients (31.5%) were hypothermic (below/

NON-PARAMETRIC CORRELATION BETWEEN CLINICAL
GRADE AND EEG GRADE IN VARIOUS DRUG GROUPS.

DRUG GROUP	Tau	Corrected z	p
BARBITURATE	0.76	2.68	0.004
MANDRAX	0.90	2.76	0.003
TRICYCLIC COMPOUNDS	0.81	2.36	0.01
MISCELLANEOUS (OR) OTHER	0.85	2.62	0.004
ALL DRUGS *	0.85	2.87	0.002

* Note the overall correlation was calculated seperately and not obtained by averaging individual correlation.

TABLE 28.

TEMPERATURE (°C) ON ADMISSION AND DRUG
GROUP OF 127 PATIENTS.

DRUG	NUMBER OF CASES						40.0+	TOTAL
	TEMPERATURE (°C)							
	32.2	32.3	34.5	35.6	37.9	39.0		
		to	to	to	to	to		
		34.4	35.5	37.8	38.9	39.9		
BARBITURATES	2	5	10	31	1	1	-	50
MANDRAX	-	2	5	16	-	-	-	23
NITRAZEPAM	-	-	-	19	-	-	-	19
TRICYCLIC COMPOUNDS	-	1	4	5	-	-	-	10
OTHERS	1	2	8	14	-	-	-	25
TOTAL	3	10	27	85	1	1	-	127

TABLE 29

(below 35.5°C) and of these 13 were below 34.5°C and three (2 from the barbiturate group and one from the miscellaneous group) below 32.3°C . Only two patients (1.5%) were hyperthermic. Both were from the barbiturate group; one had a temperature of 37.8°C and the other 39.0°C . A significant negative correlation (Table 30) between the temperature and EEG grade was found ($p = 0.01$) for all the drugs. This implies that hypothermia was associated with EEG coma grades IV-VII.

In the barbiturate group (Table 29) patients who had taken an overdose of medium or short acting barbiturates seemed especially to be liable to hypothermia, with temperatures below 35.6°C , namely, in the pentobarbitone group, 3 of 6, in the quinalbarbitone group, 3 of 7, and in the Tuinal group, 3 of 7. A correlation between temperature and EEG grades of barbiturate coma (Table 30) was found to be significant ($p = 0.01$).

A correlation between temperature and EEG grades was then calculated separately for other drug groups (Table 30) and was found to be significant for Mandrax ($p = 0.001$) and miscellaneous (other) drug ($p = 0.001$) groups.

IV.M.

TOTAL PERIOD OF UNCONSCIOUSNESS:-

An estimate of the total period of coma was made for the unconscious patients. The period of unconsciousness was considered to commence from the time of ingestion of the poison, as given in the history by informants and later ascertained from the patient.

One/

NON-PARAMETRIC CORRELATION BETWEEN THE
TEMPERATURE AND EEG GRADE IN VARIOUS
DRUG GROUPS.

DRUG GROUP	Tau	Corrected z	p
BARBITURATE	-0.29	-2.35	0.01
MANDRAX	-0.38	-2.33	0.001
TRICYCLIC	-0.30	-1.78	0.04
MISCELLANEOUS OR OTHER	-0.44	-3.26	0.001
ALL DRUGS *	-0.38	-2.36	0.01

* Note the overall correlation was calculated separately and not obtained by averaging individual correlation.

TABLE 30.

One hundred and five patients were unconscious on admission to the hospital. One hundred and one regained consciousness; 4 died. The distribution of coma duration for patients in each group is presented in Table 31. Twenty nine of 105 patients (27.5%) were in coma for less than 13 hours and 53 patients (50.5%) for 13-48 hours. Twenty three patients (22%) were unconscious for more than 48 hours, 12 for less than 72 hours, 6 for 73-95 hours and 5 patients (2 from the barbiturate group and 3 from the Mandrax group) for more than 95 hours. Of the 23 patients who were unconscious for more than 48 hours, 16 had taken barbiturates, 5 Mandrax and two miscellaneous (other) drugs. The correlation between the total duration of coma and the EEG grade of coma for all the drug groups (Table 32) was found to be significant ($p = 0.01$). Similarly a significant correlation ($p = 0.01$) was observed for the barbiturate group alone.

All the patients in the tricyclic compounds group (Table 31) were in coma for less than 48 hours. Only one of the 10 patients in this group was in coma for more than 24 hours, while 6 were unconscious for less than 24 hours and 3 for less than 12 hours. A significant ($p = 0.03$) correlation was found between the duration and the EEG grade of coma (Table 32). The correlation for miscellaneous (other) drug group (Table 32) was also significant ($p = 0.03$).

IV.N.

BLOOD DRUG LEVELS:-

Serum barbiturate levels were estimated in 49 of 50 patients with acute barbiturate poisoning (Tables 39 and 40). One patient/

TOTAL PERIOD OF COMA (HOURS) AND DRUG INGESTED
IN 105 CASES UNCONSCIOUS ON ADMISSION.

DRUG GROUP	NUMBER OF CASES DURATION (HOURS) OF COMA						TOTAL
	12	13-24	25-48	49-72	73-95	96+	
BARBITURATES	11	8	15	10	4	2	50
MANDRAX	10	4	4	1	1	3	23
NITRAZEPAM	-	-	-	-	-	-	-
TRICYCLIC COMPOUNDS	3	6	1	-	-	-	10
OTHERS	5	8	7	1	1	-	22
TOTAL	29	26	27	12	6	5	105

TABLE 31.

**NON-PARAMETRIC CORRELATION BETWEEN DURATION
OF COMA AND EEG GRADE OF COMA IN VARIOUS
DRUG GROUPS.**

DRUG GROUPS	Tau	Corrected z	p
BARBITURATE	0.62	2.32	0.01
MANDRAX	0.28	0.96	0.17
TRICYCLIC COMPOUNDS	0.63	1.94	0.03
MISCELLANEOUS OR OTHER	0.48	1.86	0.03
ALL DRUGS *	0.58	2.35	0.01

* Note the overall correlation was calculated separately and not obtained by averaging individual correlation.

TABLE 32.

patient who had taken barbitone had a record level of 67.0 mg.%, A significant ($p = 0.007$) correlation was found between blood drug levels of the long acting barbiturates and EEG grade (Table 36).

In the tricyclic antidepressant group estimation of the drug in the blood was carried out only in one patient (Case No. 95) and she had 116 μ g. percent of amitriptyline on admission. This subsequently rose to a maximum of 147 μ g. percent. In the nitrazepam group Case No. 78 had a blood nitrazepam level of 65 μ g.% and in another patient (Case No. 86) urine examination confirmed the presence of the drug.

Blood methaqualone estimation was done in all cases except 2. However, for these 2 cases the history from informants, prescriptions issued by the family doctor, the presence of clinical signs such as increased tone in the muscles and increased tendon reflexes, and, on recovery, confirmation by the patient, suggested that they had taken Mandrax. Of the remaining 21 patients, on admission nine had a blood methaqualone level of up to 2.9 mg. percent. In eight patients it was 3.0 - 4.9 mg.%, two had 5.0 to 6.9 mg.% and two had more than 7.0 mg.%.

In four cases (Cases Nos. 54, 59, 60 and 74) the blood methaqualone level later rose to a level higher than that estimated on admission. It rose to a maximum of 7.6, 12.9, 3.2 and 11.7, from 4.9, 9.0, 2.2 and 4.1 mg.% respectively. Blood methaqualone levels and EEG grade were significantly correlated ($p = 0.01$).

IV.0

BARBITURATE POISONING:-

Fifty patients, 15 men and 35 women, came into this group/

group (Table 33). All recovered. Three (Case Nos. 8, 27 and 39) had a cardiac arrest of less than 90 seconds but were resuscitated and serial electrocardiograms showed no evidence of myocardial damage. Ten patients required assisted ventilation, of whom four needed the respirator for less than 5 hours, five for 6-12 hours and one for 13 hours. Three patients (Case Nos. 5, 14 and 39) were treated with forced alkaline diuresis and the remainder were given intensive supportive therapy. Five patients (Case Nos. 6, 8, 34, 41 and 47) had also taken alcohol. The blood alcohol concentration in patient No. 8 was 62 mg.%.

The findings from the initial EEG recording for patients in each barbiturate preparation group are tabulated in Table 34. These grades do not take account of subsequent deterioration or improvement in the EEG record. Forty percent (20 of 50) of this group were Grades V-VII; all the 7 cases of quinalbarbitone poisoning were in this "deep" coma range. In contrast the majority of patients who took phenobarbitone (12 of 13) were Grades II-IV; only one phenobarbitone patient was Grade V.

Complete electrical silence (or isoelectric record) lasting from three hours (Case No. 36) to 28 hours (Case No. 27) was seen in eight cases. In five of these it was seen in the initial record, whereas in the remaining three it was observed sometime after the beginning of the initial recording. Of the 5 patients who had an isoelectric record on initial recording, three had taken quinalbarbitone, one butobarbitone and one barbitone.

The/

SEX DISTRIBUTION AND BARBITURATE INGESTED
IN 50 PATIENTS.

BARBITURATE PREPARATION	NUMBER OF PATIENTS		
	MALE	FEMALE	TOTAL
PHENOBARBITONE	5	8	13
BARBITONE	1	1	2
AMYLOBARBITONE	2	6	8
BUTOBARBITONE	1	3	4
QUINALBARBITONE	2	5	7
PENTOBARBITONE	3	3	6
CYCLOBARBITONE	-	3	3
TUINAL	1	6	7
TOTAL	15	35	50

TABLE 33.

EEG ABNORMALITY AND BARBITURATE
INGESTED BY 50 PATIENTS.

BARBITURATE PREPARATION	EEG GRADES OF COMA							TOTAL
	I	II	III	IV	V	VI	VII	
PHENOBARBITONE	-	5	4	3	1	-	-	13
BARBITONE	-	1	-	-	-	-	1	2
AMYLOBARBITONE	-	1	2	3	1	1	-	8
BUTOBARBITONE	-	-	-	3	-	-	1	4
QUINALBARBITONE	-	-	-	-	2	2	3	7
PENTOBARBITONE	-	-	-	3	1	2	-	6
CYCLOBARBITONE	-	-	1	1	-	1	-	3
TUINAL	-	1	1	1	3	1	-	7
TOTAL	-	8	8	14	8	7	5	50

TABLE 34

The ages of these patients can be seen in Table 35. Eighty percent of the patients in this group (42 out of 50) were 20-59 years old. The correlation between age group and the EEG grade of coma (Table 36) was not significant.

Clinical assessment of depth of coma at the time of admission to the ward is shown in Table 37. Most of the patients (12 of 13) who had taken phenobarbitone were grades 1 and 2, whereas the majority of the patients taking other barbiturate preparations were grades 3 and 4. For example, 6 of the 7 who had taken quinalbarbitone and 5 of the 6 who had taken pentobarbitone were Grade 4. All the patients who had taken butobarbitone, quinalbarbitone or pentobarbitone were grades 3 and 4. The correlation between clinical assessment of depth of coma and the EEG depth of coma (Table 36) was significant ($p = 0.002$).

The frequency distribution of rectal temperature for the barbiturate group is shown in Table 38. Thirty four percent (17 of 50) of patients were hypothermic (below 35.5°C) while only 4% (2 of 50) were hyperthermic. Patients who had taken an overdose of medium or short-acting barbiturates seemed especially to be liable to hypothermia with temperature below 35.6°C . Six out of the thirteen patients who had taken either quinalbarbitone or pentobarbitone were hypothermic whereas only 11 of the remaining 37 patients were hypothermic. This difference however is not significant ($\chi^2 = 0.5$; $df = 1$). The majority of phenobarbitone cases (11 of 13) had a temperature/

AGE IN YEARS OF PATIENTS AND BARBITURATE INGESTED

BARBITURATE PREPARATION	NUMBER OF PATIENTS AGE IN YEARS					TOTAL
	-19	20-39	40-59	60-79	80 +	
PHENOBARBITONE	1	6	6	-	-	13
BARBITONE	-	-	1	1	-	2
AMYLOBARBITONE	1	4	3	-	-	8
BUTOBARBITONE	-	3	1	-	-	4
QUINALBARBITONE	-	2	4	-	1	7
PENTOBARBITONE	-	3	3	-	-	6
CYCLOBARBITONE	-	1	-	2	-	3
TUINAL	-	3	2	2	-	7
TOTAL	2	22	20	5	1	50

TABLE 35

NON-PARAMETRIC CORRELATION BETWEEN EEG GRADE OF COMA
AND OTHER PARAMETERS IN FIFTY CASES OF ACUTE
BARBITURATE POISONING.

PARAMETERS	Tau	Corrected z	p
AGE GROUP AND EEG GRADE	0.22	1.14	0.13
CLINICAL GRADE AND EEG GRADE	0.76	2.68	0.004
TEMPERATURE AND EEG GRADE	-0.29	-2.35	0.01
DURATION OF COMA AND EEG GRADE	0.62	2.32	0.01
EEG GRADES AND SERUM LEVELS OF MEDIUM AND SHORT ACTING BARBITURATE	0.17	0.97	0.17
SERUM LEVELS OF LONG-ACTING BARB- ITURATES AND EEG GRADES	0.74	2.34	0.001

TABLE 36

CLINICAL ASSESSMENT OF DEPTH OF COMA AND
BARBITURATE PREPARATION INGESTED BY 50 PATIENTS.

BARBITURATE PREPARATION	NUMBER OF PATIENTS					TOTAL
	CLINICAL GRADE OF COMA					
	0	1	2	3	4	
PHENOBARBITONE	-	6	6	1	-	13
BARBITONE	-	1	-	-	1	2
AMYLOBARBITONE	-	1	1	4	2	8
BUTOBARBITONE	-	-	-	2	2	4
QUINALBARBITONE	-	-	-	1	6	7
PENTOBARBITONE	-	-	-	1	5	6
CYCLOBARBITONE	-	-	1	1	1	3
TUINAL	-	1	-	2	4	7
TOTAL	-	9	8	12	21	50

TABLE 37

TEMPERATURE AND BARBITURATE INGESTED BY
50 PATIENTS.

BARBITURATE PREPARATION	NUMBER OF PATIENTS							TOTAL
	TEMPERATURE IN CENTIGRADE							
	-32.2 to 34.4	32.3 to 34.4	34.5 to 35.5	35.6 to 37.8	37.9 to 38.9	39.0 to 39.9	40.0 +	
PHENOBARBITONE	-	-	1	11	1	-	-	13
BARBITONE	-	-	1	1	-	-	-	2
AMYLOBARBITONE	-	-	3	5	-	-	-	8
BUTOBARBITONE	1	-	1	2	-	-	-	4
QUINALBARBITONE	-	1	2	3	-	1	-	7
PENTOBARBITONE	1	1	1	3	-	-	-	6
CYCLOBARBITONE	-	1	-	2	-	-	-	3
TUINAL	-	2	1	4	-	-	-	7
TOTAL	2	5	10	31	1	1	-	50

TABLE 38

temperature in the range of 35.6°C to 37.8°C . A significant correlation was found (Table 36) between temperature and the EEG grade of coma ($p = 0.007$).

The serum barbiturate levels of fifteen patients who took long-acting barbiturates (phenobarbitone or barbitone) are shown in Table 39. Seventy three percent (11 of 15) of cases had a blood drug level of more than 8.0 mg.%. Sixty two percent (8 of 13) of phenobarbitone cases had a blood drug level in the range of 8.0 - 14.9 mg.%. One patient in the barbitone group had a record level of 67.0 mg.%. She had an isoelectric EEG tracing and was treated with forced alkaline diuresis. Blood drug levels of the long acting barbiturates and EEG grade (Table 36) were significantly correlated ($p = 0.007$).

The serum concentration of medium and short-acting barbiturates is presented in Table 40. In 17 of the 35 cases the serum levels were 2.9 mg.% or less. Only 5 of the 25 cases had a serum level of more than 5.0 mg.%. In one case (of amylobarbitone) the level of drug in the blood was not estimated.

The period of unconsciousness following the ingestion of barbiturates by the fifty patients is shown in Table 41. Fifty percent of cases (25 of 50) were in coma for 25 to 72 hours, 38% less than 25 hours and 12% more than 72 hours. Only two patients (both from the phenobarbitone group) were in coma for more than 96 hours. The correlation between the total period of unconsciousness and the EEG grade of coma (Table 36) was significant ($p = 0.001$).

PHENOBARBITONE AND BARBITONE CONCENTRATION
IN BLOOD (mg. PER 100 ml.) IN 15 PATIENTS.

	MG. PERCENT BLOOD LEVEL					TOTAL
	Mg. Blood Level					
	N.K.	4.9	5-7.9	8-14.9	15 +	
PHENOBARBITONE	-	1	3	8	1	13
BARBITONE	-	-	-	1	1	2
TOTAL	-	1	3	9	2	15

TABLE 39

MEDIUM AND SHORT ACTING BARBITURATE BLOOD
CONCENTRATION (mg. per 100 ml.) IN 35 PATIENTS.

BARBITURATE PREPARATION	Mg. % BLOOD LEVEL					TOTAL
	N.K.	-2.9	3-4.9	5-6.9	7+	
AMYLOBARBITONE	1	4	2	-	1	6
BUTOBARBITONE	-	-	3	-	1	4
QUINALBARBITONE	-	4	1	2	-	7
PENTOBARBITONE	-	3	3	-	-	6
CYCLOBARBITONE	-	1	1	-	1	3
TUINAL	-	5	2	-	-	7
TOTAL	1	17	12	2	3	35

TABLE 40.

TOTAL PERIOD OF COMA (HOURS) AND
BARBITURATE INGESTED.

BARBITURATE PREPARATION	HOURS IN COMA						TOTAL
	-12	13-24	24-48	49-72	73-95	96+	
PHENOBARBITONE	6	-	3	2	-	2	13
BARBITONE	1	-	-	1	-	-	2
AMYLOBARBITONE	1	3	3	-	1	-	8
BUTOBARBITONE	-	1	2	-	1	-	4
QUINALBARBITONE	-	1	2	3	1	-	7
PENTOBARBITONE	-	1	3	1	1	-	6
CYCLOBARBITONE	1	-	1	1	-	-	3
TUINAL	2	2	1	2	-	-	7
TOTAL	11	8	15	10	4	2	50

TABLE 41.

IV. P.

SELECTED CASE HISTORIES.

PROJECT NO. 2.

CASE HISTORY No. 1 (11/103/CQ).

A 28 year old female was admitted to the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh at 11.40 hours on the 8th March 1969, after having taken a large number of phenobarbitone tablets two hours prior to admissions.

Course in the Hospital:-

On admission to the ward she was drowsy and unable to give any history. Physical examination did not reveal any abnormality. Her pulse was 80 per minute and regular. Blood pressure 100/60 mm.Hg. and rectal temperature 37.0°C. Stomach washout was performed on admission, with some tablet material being noticed in the return but by now she was deeply unconscious, making no response to rubbing of the sternum with the knuckles. Blood phenobarbitone level four hours after drug ingestion was 9.2 mg.%. Her first electroencephalogram (EEG) record (Fig. 21) taken four hours after she became comatose, contained background $\frac{1}{2}$ -1 cps activity with superimposed fast activity of 9-10 cps (Grade IV). Continuous EEG monitoring was done throughout the period of coma and for a period afterwards.

Clinically her condition remained unchanged for 24 hours and her blood phenobarbitone level rose to 9.5 mg.%. Her EEG tracing after eight hours of coma (Fig. 22) revealed bursts of slow wave activity at $\frac{1}{2}$ -1 cps activity on which was superimposed fast activity of 9-10 cps. Alternating with these slow/

EEG IN ACUTE PHENOBARBITONE POISONING.

(Patient 11, Female 28 years old)

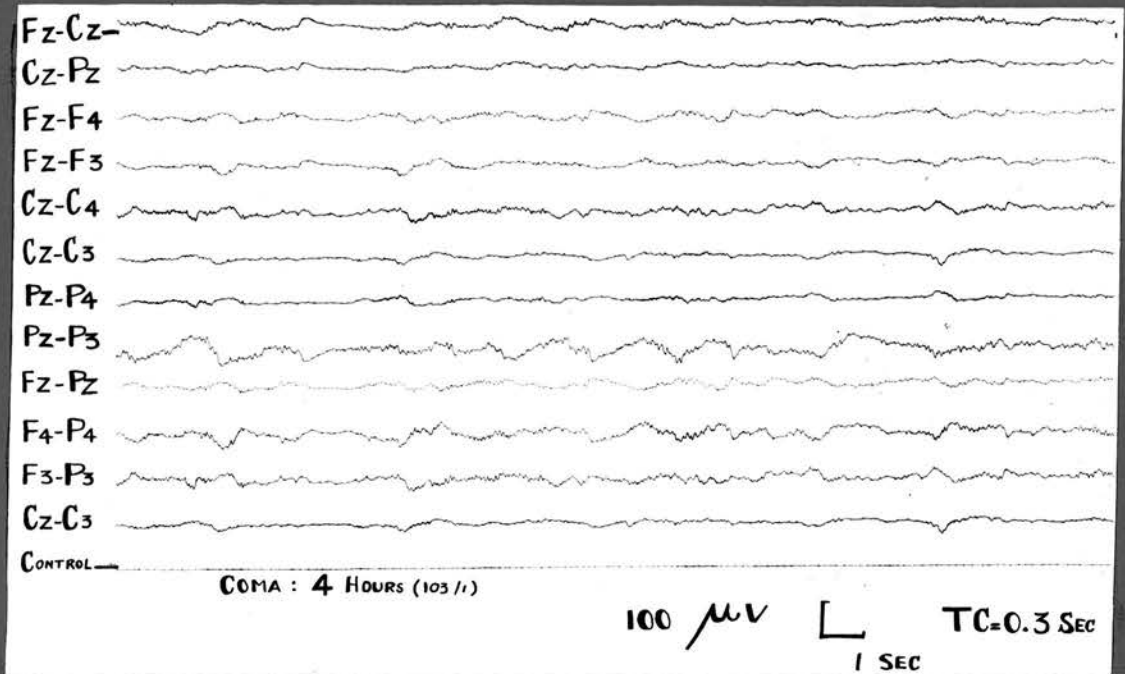


Figure 21:

Grade IV EEG abnormality. Background activity of $\frac{1}{2}$ -1 cps with superimposed 9-10 cps activity.

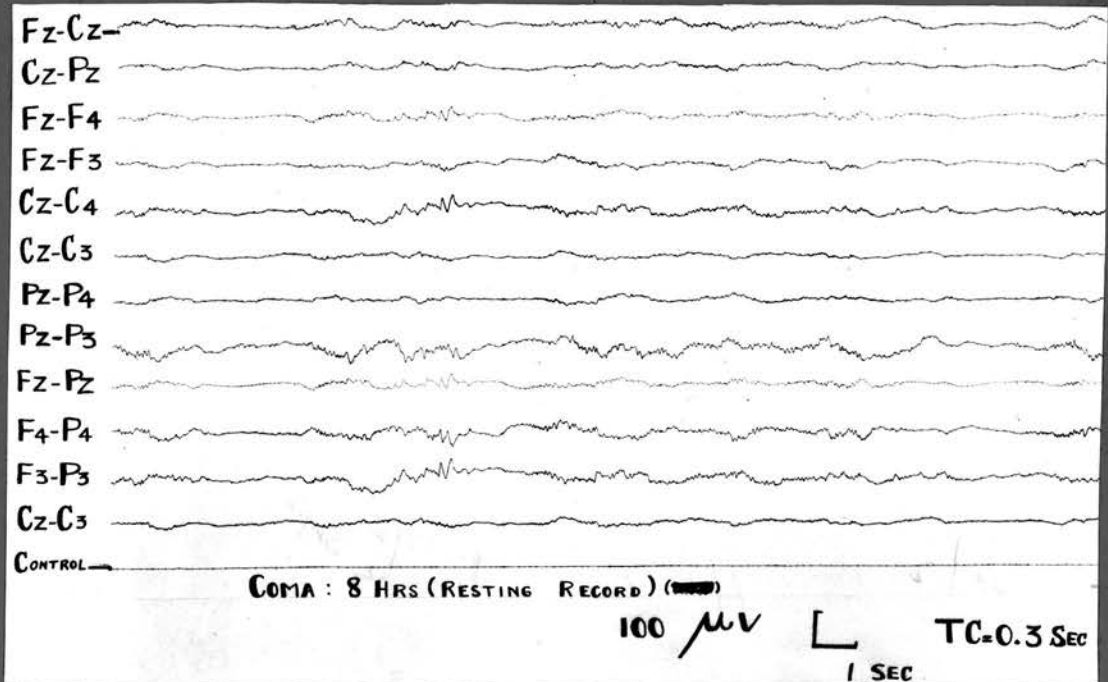


Figure 22:

After eight hours of coma EEG record showed bursts of $\frac{1}{2}$ -1 cps activity, alternating with these slow waves were distinct areas of less activity.

slow waves were areas of less activity of 2-4 seconds duration, thus showing a deterioration in the condition of the patient as judged by the electrical activity of the brain. On sternal stimulation no clinical response was observed, but the EEG record (Fig. 23) showed a response, namely the areas of less activity disappeared and slow wave activity increased both in frequency and amplitude. Background activity was now dominantly $\frac{1}{2}$ -2 cps mixed with some 2-4 cps. This reactivity disappeared after 100 second and the record once again contained slow wave bursts with intervening flat areas.

Little change was noticed in the EEG record over the next 18 hours till after 30 hours of coma. The EEG record revealed almost continuous slow wave activity at $\frac{1}{2}$ -1 cps (Grade IV). The intervening flat EEG periods gradually disappeared. Clinically the patient's condition remained the same and no clinical response was noticeable to sternal stimulation but the EEG record continued to show gradual improvement. After 40 hours of coma the EEG record (Fig. 24) contained dominant activity at $\frac{1}{2}$ -2 cps mixed with which was some activity at 2-4 cps. The superimposed fast activity was now absent. On stimulating reactivity was noticed in the form of disappearance of some of the large slow component of the record with replacement by faster frequencies of 2-4 cps.

Forty seven hours after the ingestion of the drug the patient first showed a clinical response to a maximal painful stimulus. Her blood phenobarbitone level was 9.7 mg. percent. After/

EEG IN ACUTE PHENOBARBITONE POISONING

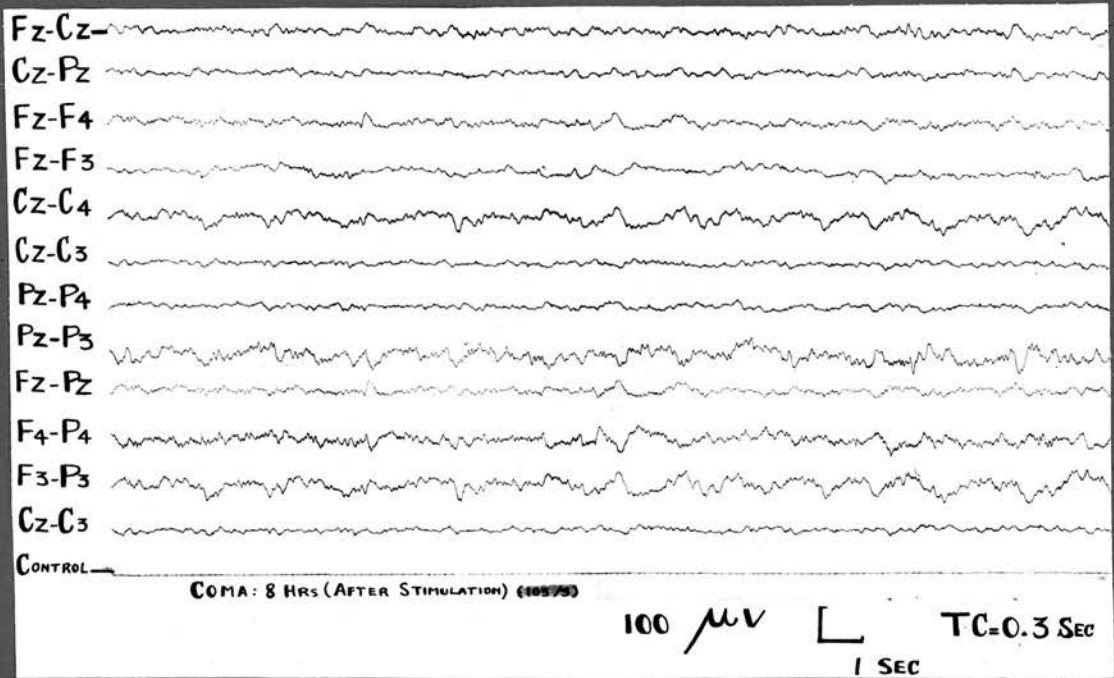


Figure 23:

After stimulation areas of less activity disappeared and EEG consisted of dominant activity at $\frac{1}{2}$ -2 cps mixed with some 2-4 cps activity.

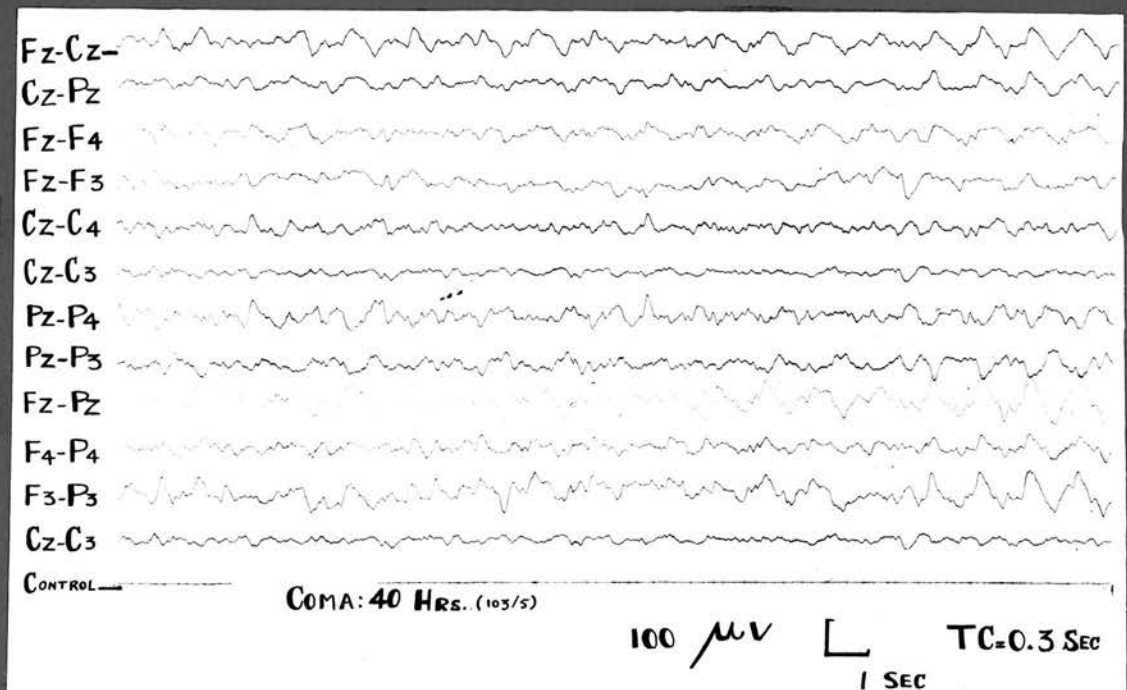


Figure 24:

Forty hours after lapsing into coma the dominant activity was $\frac{1}{2}$ -2 cps mixed with some 2-4 cps activity. The superimposed fast activity was now absent.

After 52 hours of coma her EEG record (Fig. 25) contained $\frac{1}{2}$ -2 cps slow wave activity, superimposed on which was some 6-8 cps fast activity.

Alternating periods of slow waves and faster frequencies appeared spontaneously and the patient produced such "spontaneous shifts" without being stimulated (Fig. 26). Each spontaneous shift was characterized by two phases. In the one there were large slow waves at $\frac{1}{2}$ -1 cps but with only little superimposed fast frequency, this phase would last for 40-50 seconds and give way to 1-4 cps activity with little superimposed fast activity (Fig. 27).

An EEG tracing after 76 hours of coma (Fig. 28) showed dominant delta activity together with some theta (Grade III). An EEG tracing after 84 hours of coma (Fig. 29) showed low voltage slow waves and increased amount of 4-6 cps activity (Grade III). After 92 hours of coma (Fig. 30) only a small number of slow waves at 2-4 cps were seen and the dominant activity was 5-8 cps (Grade III).

After remaining deeply unconscious and virtually unresponsive for four days she regained consciousness 96 hours after drug ingestion, but was drowsy. On the 6th hospital day she was still drowsy, her blood phenobarbitone level was 7.9 mg.%. She was seen by the psychiatrist who transferred her to the North Wing of the Royal Edinburgh Hospital for inpatient psychiatric care.

Her blood examination for phenobarbitone concentration was reported to be 4.2 mg.% on the 10th day after the drug ingestion, 3.4 mg. on the 11th and 2.8 mg.% on the 12th day; 2.7 mg. on the 13th, 2.5 mg. on the 14th, and 1.5 mg. on the 17th day and 0.8 mg.% on the 19th day after ingestion of the drug, when she asked for her discharge/

EEG IN ACUTE PHENOBARBITONE POISONING.

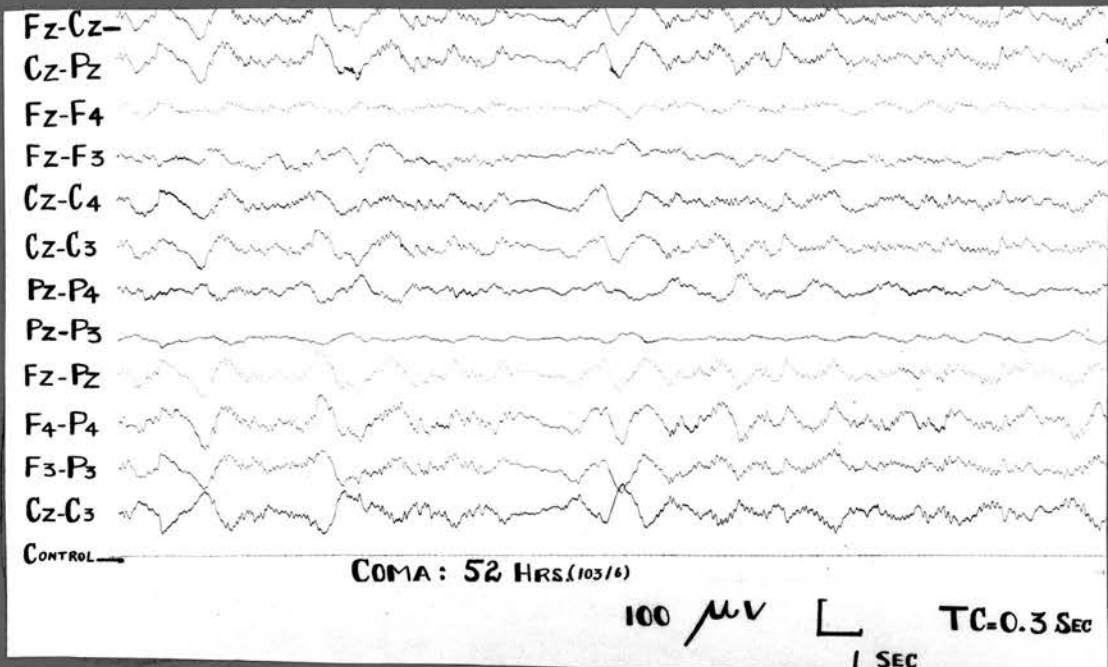


Figure 25:

After fifty two hours of coma alternate periods of high voltage $\frac{1}{2}$ -2 cps slow wave activity, superimposed on which was some 6-8 cps fast activity and low voltage faster frequencies of 6-8 cps appeared spontaneously (spontaneous shifts).

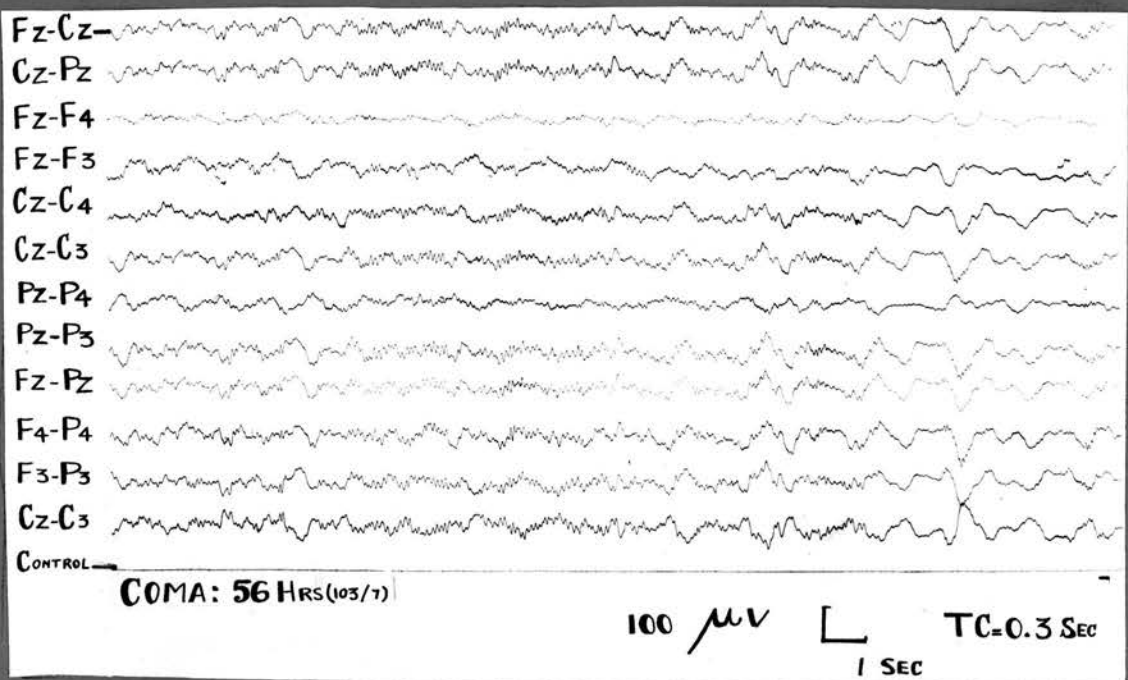


Figure 26:

Two phases of a spontaneous shift, low voltage faster frequencies of 2-4 cps with marked superimposed fast activity alternates with high voltage $\frac{1}{2}$ -1 cps slow wave activity with little superimposed fast activity.

EEG IN ACUTE PHENOBARBITONE POISONING.

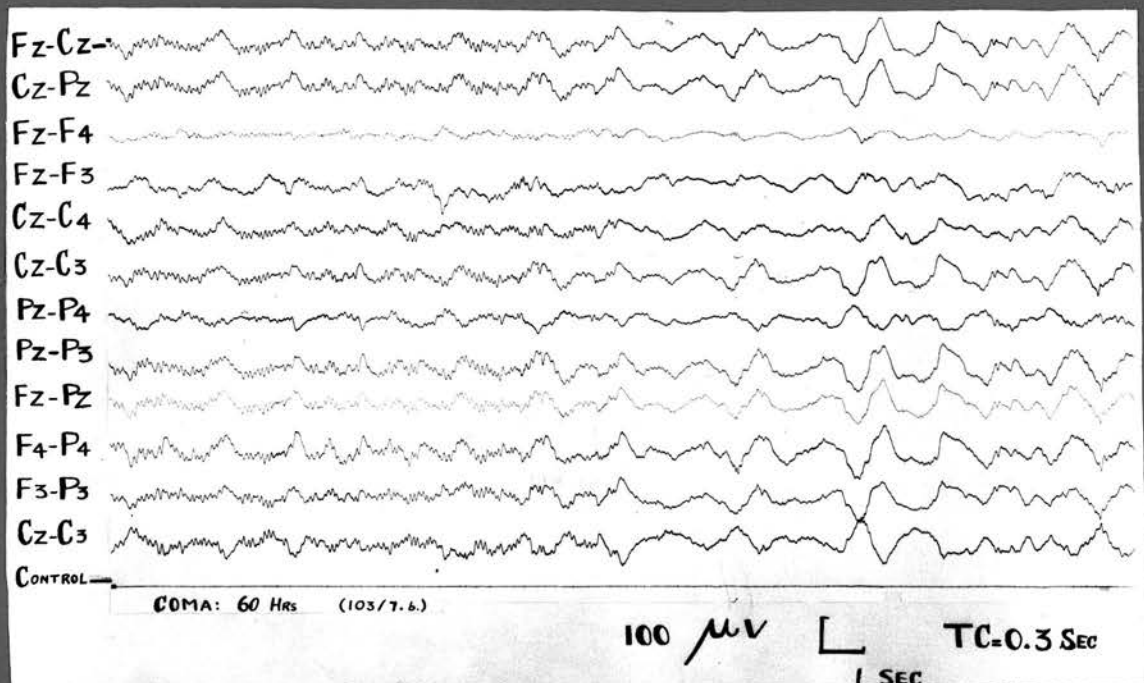


Figure 27:

Another example of a spontaneous shift. Low voltage 1-4 cps activity with superimposed 6-8 cps activity gives way to slow wave activity of $\frac{1}{2}$ -2 cps with little superimposed fast activity.

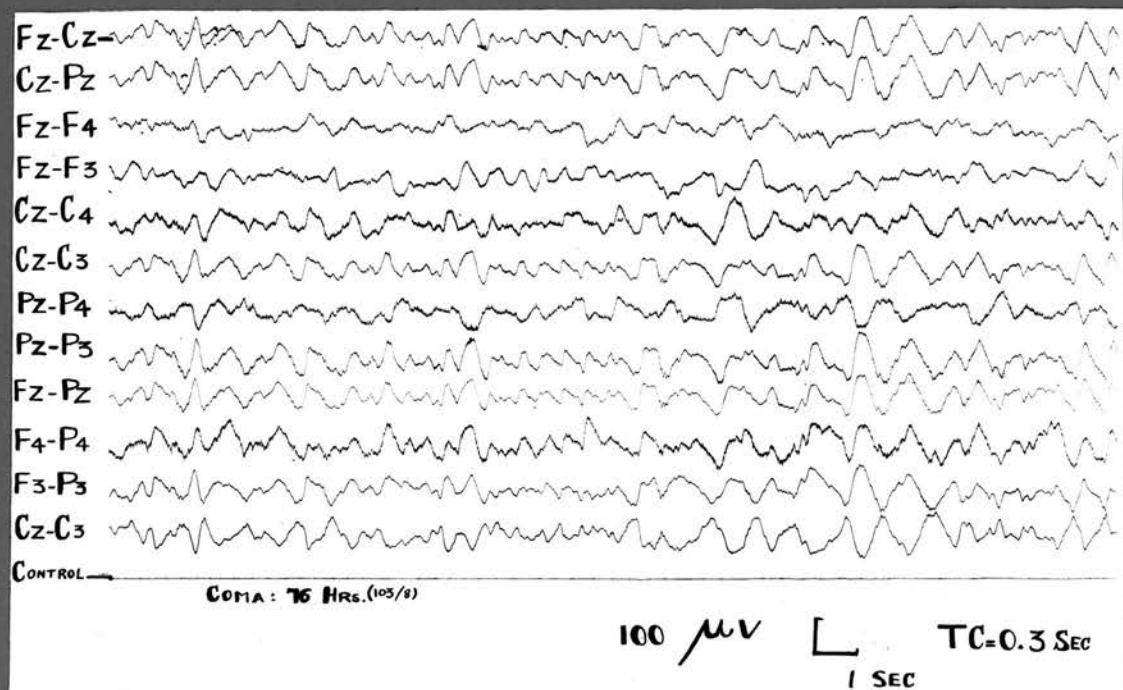


Figure 28:

After seventy six hours of coma EEG record contained high voltage dominant activity at $\frac{1}{2}$ -2 cps with some low voltage 2-4 cps activity.

EEG IN ACUTE PHENOBARBITONE POISONING.

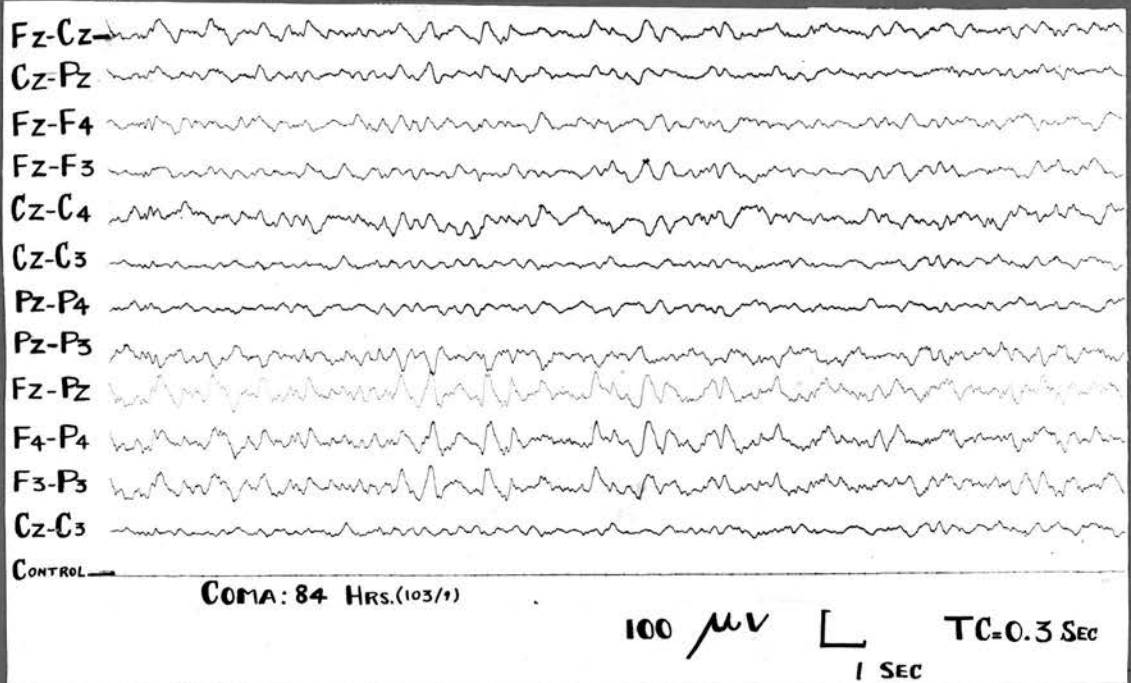


Figure 29:

EEG record after eighty four hours showed Grade III EEG abnormality. It contained dominant activity at 4-6 cps mixed with which was some low voltage 1-3 cps activity.

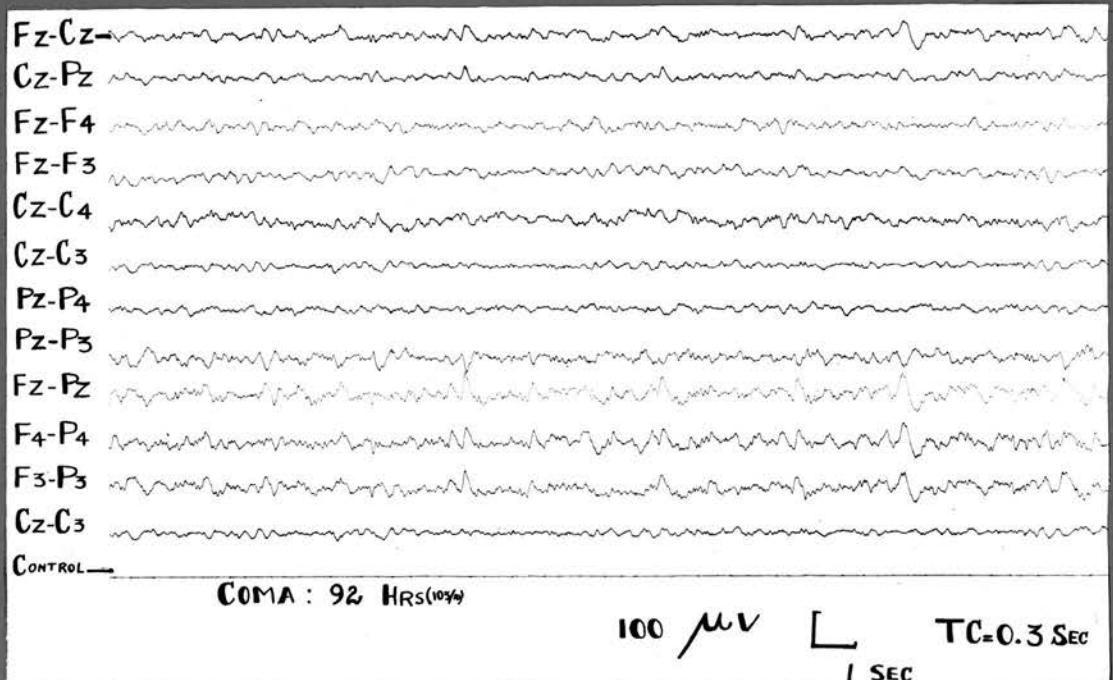


Figure 30:

After ninety two hours of coma EEG showed a predominant activity of 5-8 cps with some slow wave activity at 2-4 cps.

discharge. The further recovery of this patient (Patient No. 6) is discussed in Project No. 3. (page)

CASE HISTORY No. 2 (5/27/D.C.)

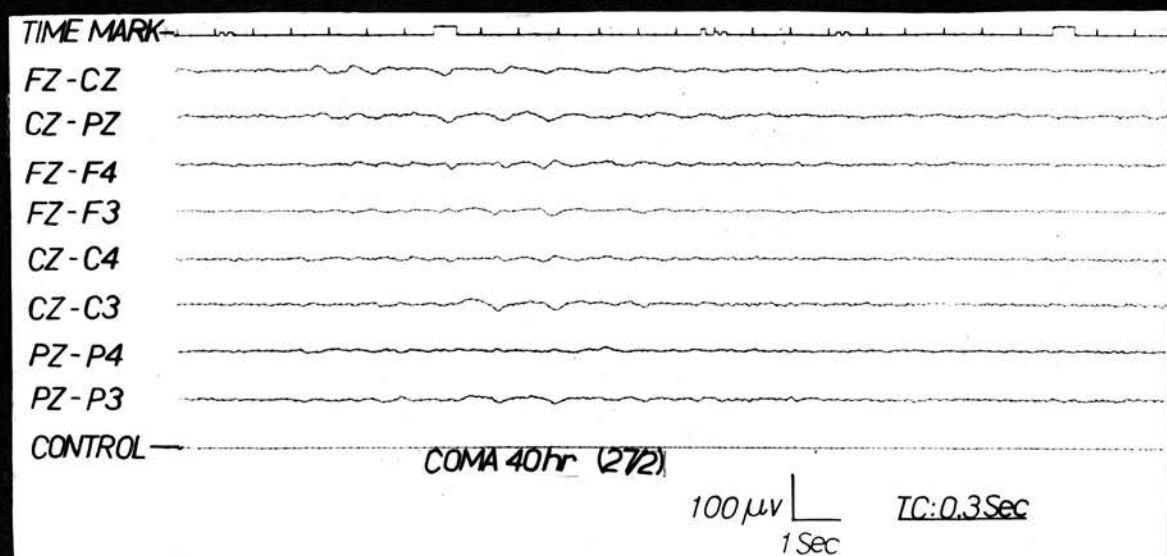
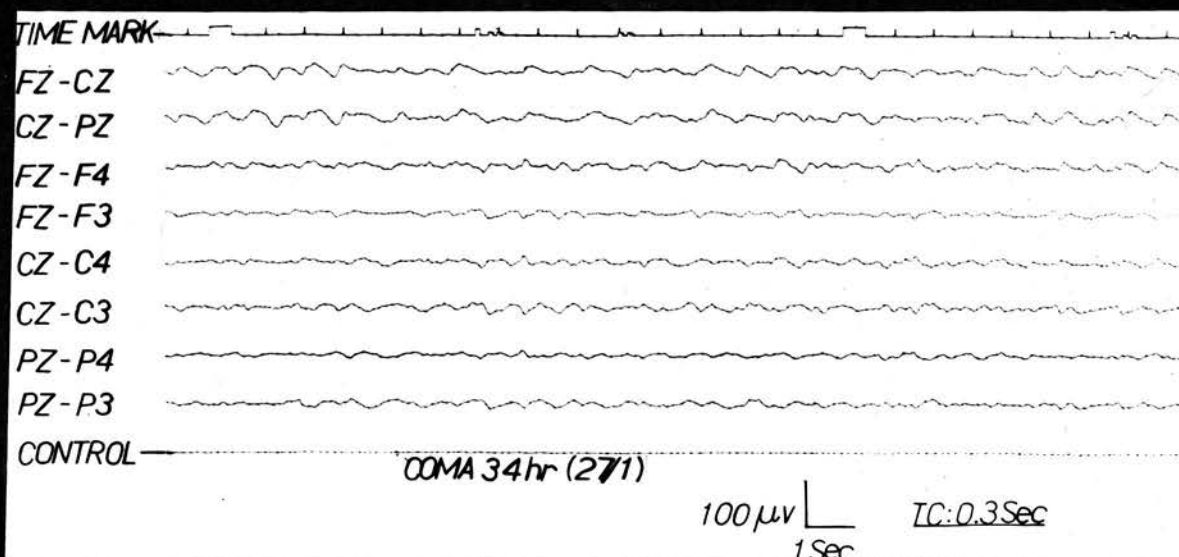
A 56 year old male was admitted at 13.45 hours on the 3rd April, 1968, having ingested 60-80 phenobarbitone tablets (60 mg. tablets).

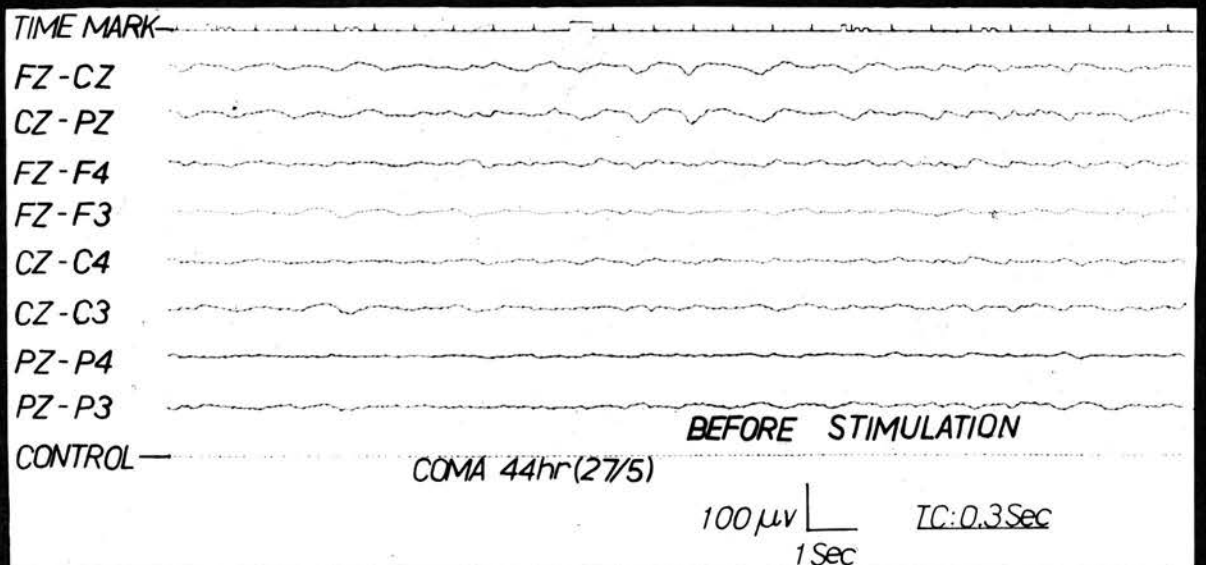
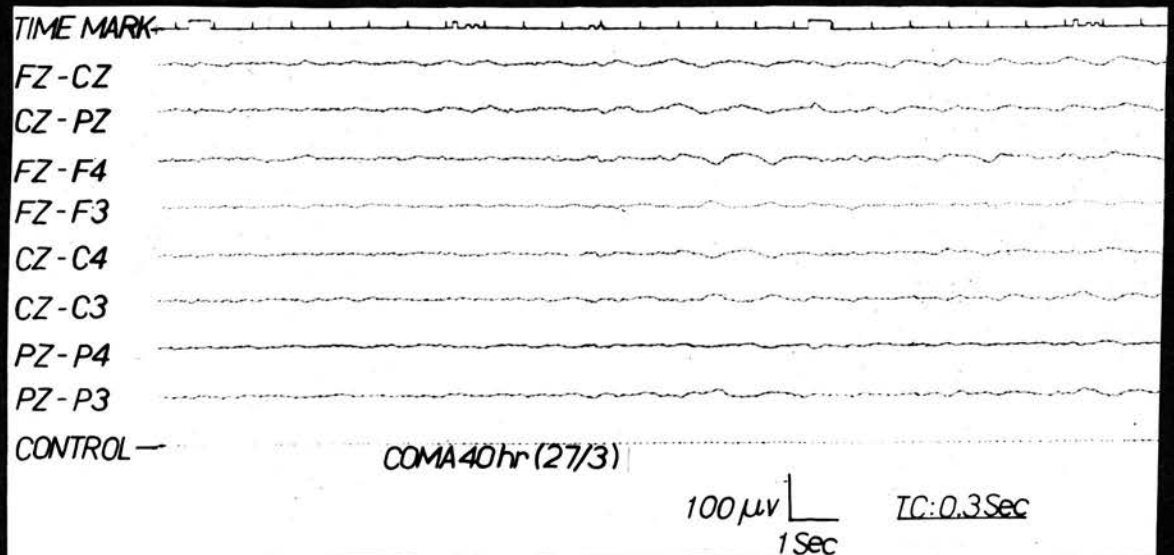
Course in the Hospital:-

On admission he was unconscious but making vigorous responses to painful stimuli. Blood pressure was 100/60 mm.Hg. and the pulse was 84 per minute, regular and of good volume. Chest examination showed scattered crepitations but in other respects a full physical examination was normal. His blood phenobarbitone concentration was 10.8 mg.%. Twelve hours after his admission his condition deteriorated and he became deeply unconscious and made minimal response to painful stimulation.

His first electroencephalographic record (Fig. 31) after 34 hours of coma revealed Grade IV EEG abnormality. Clinically his condition remained unchanged. His blood phenobarbitone level was 9.6 mg.%. Thirty five hours after the drug ingestion forced alkaline diuresis was commenced. After 40 hours of coma his EEG tracings (Fig. 32) showed burst of slow wave activity at $\frac{1}{2}$ -2 cps lasting for 4-6 seconds and the remainder of the epoch contained low voltage 4-5 cps activity. "Spontaneous shifts" were also seen when slow wave activity of several seconds duration would alternate with faster frequencies. Fig. 33 shows a transition from low voltage 4-5 cps activity to $\frac{1}{2}$ -2 cps. Superimposed fast activity was not prominent.

After/





After 44 hours of coma the patient's EEG record (Fig. 34) before stimulation showed low voltage 1-2 cps activity. After stimulation low voltage slow waves disappeared and the record (Fig. 35) now consisted of a mixture of higher voltage delta and theta waves (Grade III). Forty eight hours after lapsing into coma his EEG (Fig. 36) contained $1\frac{1}{2}$ -2 cps activity in the upper three channels and 2-4 cps in the lower channels (Grade III). His blood phenobarbitone concentration was 8.4 mg.%. Two hours later the patient made vigorous response to painful stimuli. He continued to improve and was conscious after 55 hours of coma. His blood phenobarbitone level was 8.8 mg.%.

After fifty six hours, his EEG showed a general low voltage 6-8 cps activity with bursts of slow wave activity at 1-4 cps lasting for 3-4 seconds (Grade II). One hour later when the patient was left undisturbed, his EEG record (Fig. 37) showed return of slow wave activity. This tracing contained $1\frac{1}{2}$ -3 cps activity. The upper two channels showed more slow waves and the lower six channels faster frequencies.

Sixty hours after ingestion of phenobarbitone, his EEG tracings (Fig. 38) during sleep showed a mixture of $1\frac{1}{2}$ -2 cps waves seen in the upper three channels (middle of the record) and 2-4 cps activity more marked in the lower five channels. Muscle activity was also seen. Two hours later when the patient was drowsy (Fig. 39) his record showed dominant 6-8 cps low voltage activity with bursts of low voltage 1-2 cps slow waves of 8-12 seconds duration.

Like/

EEG IN ACUTE PHENOBARBITONE POISONING.

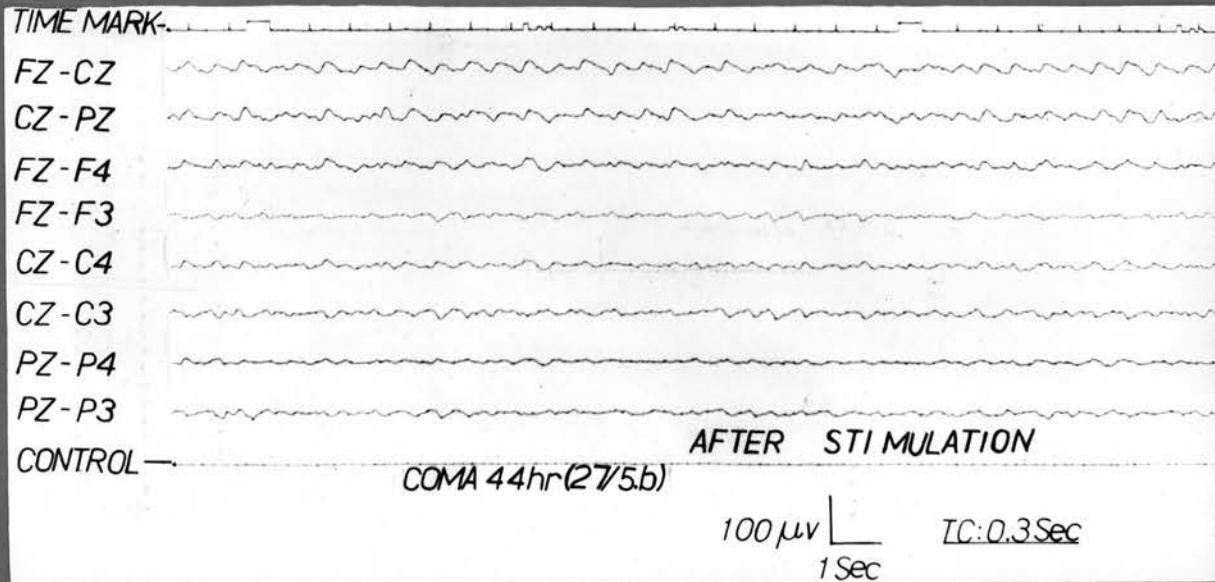


Figure 35:

After stimulation, low voltage slow waves disappeared and the record showed a mixture of higher voltage 1-2 activity and some 3-4 cps activity.

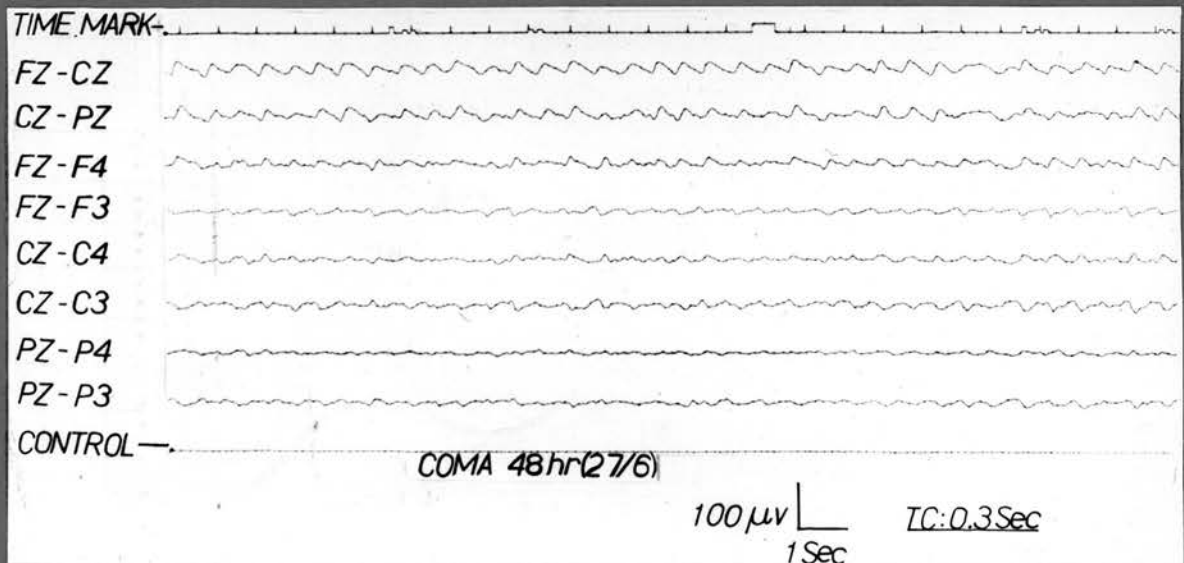


Figure 36:

After forty eight hours of coma record showed Grade III EEG abnormality. Slow waves at 1½-2 cps were seen in the upper three channels and 2-4 cps activity in the lower five channels.

EEG IN ACUTE PHENOBARBITONE POISONING.

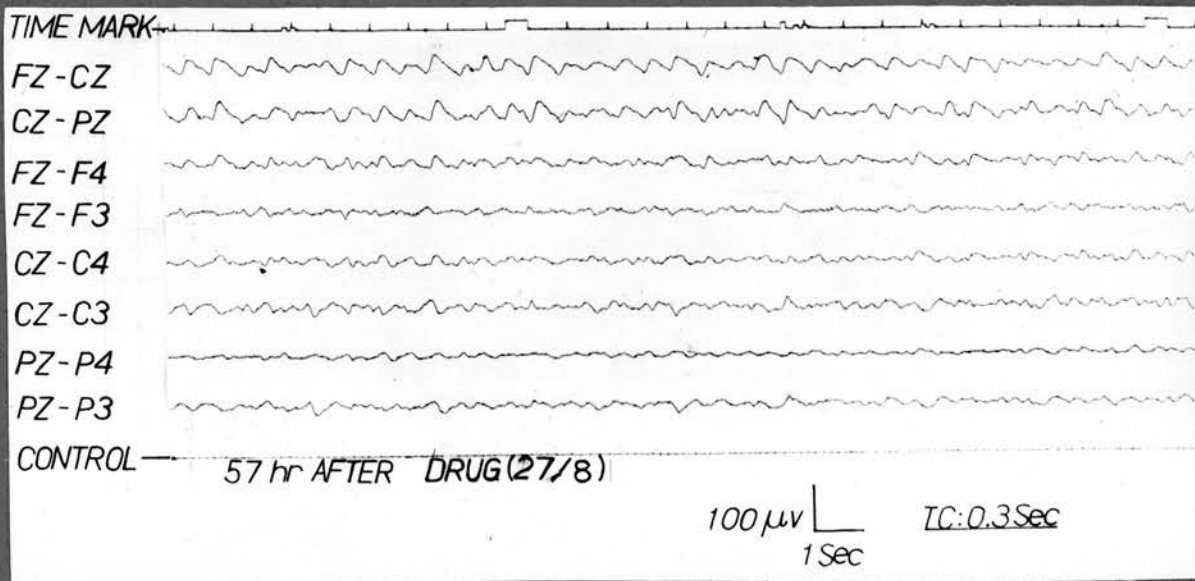


Figure 37:

When the patient was left undisturbed, he appeared asleep and his EEG showed return of slow wave activity at $1\frac{1}{2}$ -3 cps similar to the one seen in figure 36.

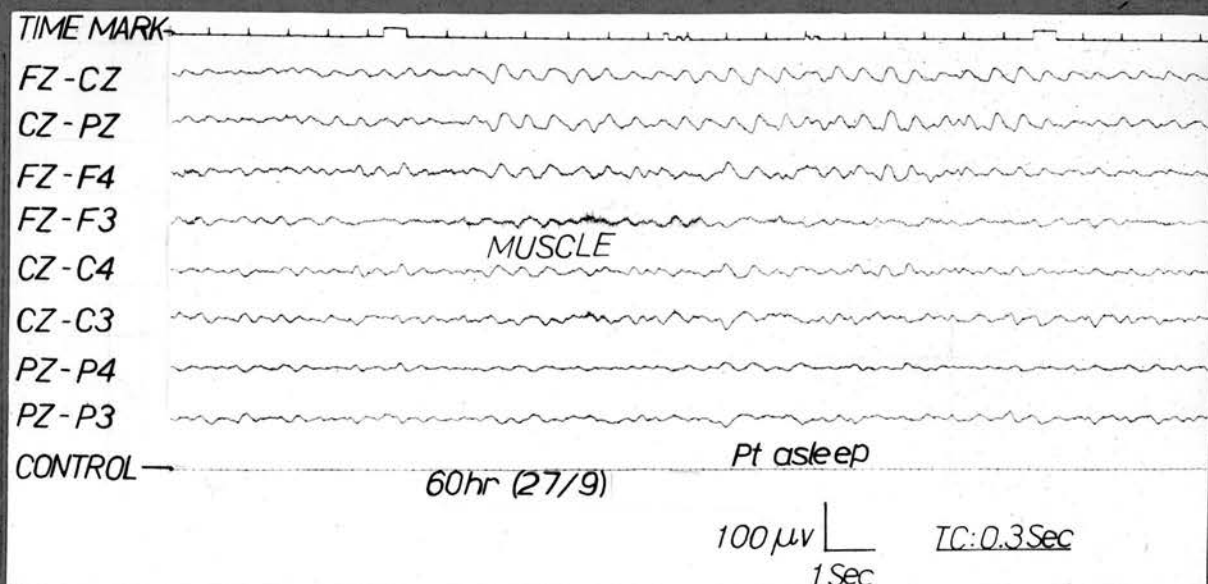


Figure 38:

A record five hours post coma when patient was asleep showed a mixture of $1\frac{1}{2}$ -2 cps waves in the upper three channels and 2-4 cps activity were marked in the lower five channels. Muscle activity was also seen.

EEG IN ACUTE PHENOBARBITONE POISONING.

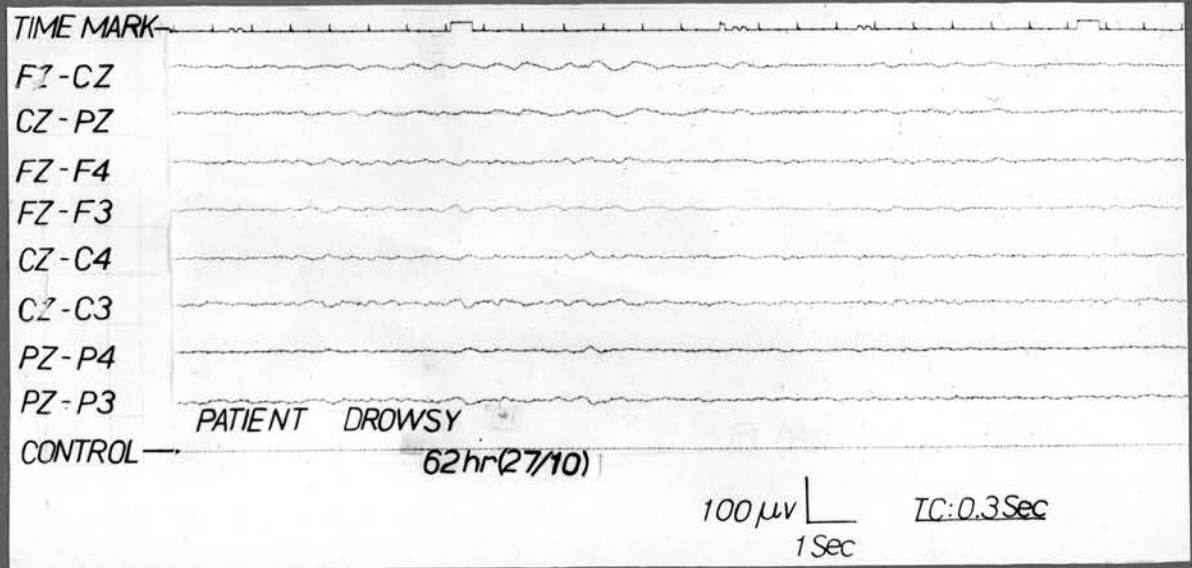


Figure 39:

Sixty two hours after ingestion of phenobarbitone (seven hours post coma) EEG record was dominated by low voltage 6-8 cps activity with a burst of low voltage 1-2 cps activity.

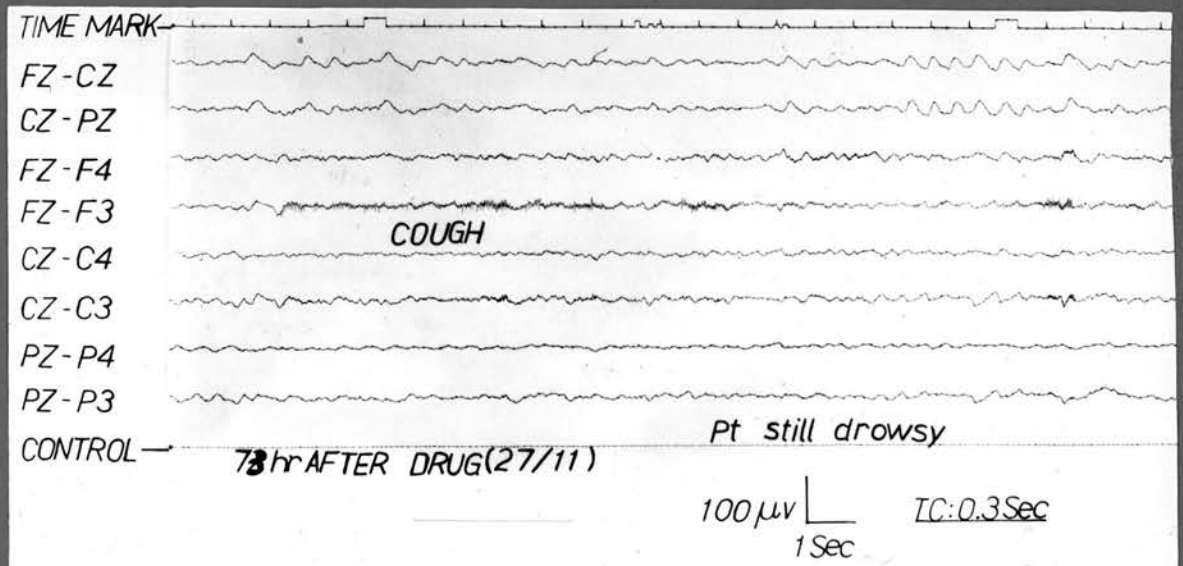


Figure 40:

Eighteen hours post coma EEG tracings showed a mixture of low voltage 2-3 cps activity and 4-6 cps activity.

Like other phenobarbitone overdose cases, although he responded to vocal command at the end of 55 hours his EEG record was abnormal for a much longer time. Seventy two hours after ingestion of drug (18 hours post-coma) the patient was still drowsy and his EEG tracings (Fig. 40) showed scattered delta and theta waves.

Upon regaining consciousness he was restless, disorientated as to time and place but gradually improved. Seventy two hours after he took the overdose he was co-operative, but anxious. His phenobarbitone level was reported to be 8.1 mg.%. Ten days after his admission he was fully recovered and was discharged on the 11th day, after having been seen by the psychiatrist.

CASE HISTORY No. 3 (14/29/J.M.)

A 64 year old woman was admitted to the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh at 09.15 hours on the 16th April, 1968, after having ingested large quantities of her sodium barbitone (Medinal) tablets 10-11 hours prior to admission.

Course of Illness in the Hospital:-

On admission she was deeply unconscious and totally unresponsive to all stimuli. Her blood pressure was 70/40 mm.Hg. and pulse 100 per minute. Chest examination showed expiratory rhonchi, but was otherwise normal as was the rest of the physical examination. An endotracheal tube was inserted and thereafter/

thereafter gastric lavage was carried out. The serum barbitone level was 67.8 mg.%. Her respiratory minute volume was 4 litres and rectal temperature 35.8°C.

Continuous electroencephalographic (EEG) monitoring was started soon after admission and her tracings (Fig. 41) showed an isoelectric record without response to any stimuli (Grade VII). Clinically she was deeply unconscious and totally unresponsive. After 14 hours of coma her blood pressure was 75/55 mm.Hg., rectal temperature 34.1°C and serum barbitone level 70 mg.%. Her EEG record (Fig. 42) was isoelectric even on maximum gain (20 micro volts per cm). Seventeen hours after ingestion of the drug her EEG record (Fig. 43) for the first time showed two isolated bursts of activity (Grade VI). Her clinical condition remained unchanged and her serum barbitone was 65 mg.%.

After 20 hours of coma her EEG (Fig. 44) showed suppression burst activity (Grade V) which increased on stimulating the sternum. Her rectal temperature was 33.0°C and serum barbitone level 65 mg.%. Twenty four hours after ingestion of the drug she was still in deep coma and did not show any clinical response to rubbing of her sternum but her EEG record (Fig. 45) showed an increase in electrical activity. Her blood barbitone level was 62 mg.% and rectal temperature 32.1°C.

After 28 hours of coma, clinically her condition remained unchanged. Her rectal temperature was 31.6°C, blood pressure 85/60 mm.Hg. and serum barbitone level 55 mg.%. Her EEG record (Fig. 46) contained abundant 4-5 cps activity without any intervening flat areas and over the next four hours this activity/

EEG AFTER BARBITONE POISONING
(Patient 14, Female, 64 years old).

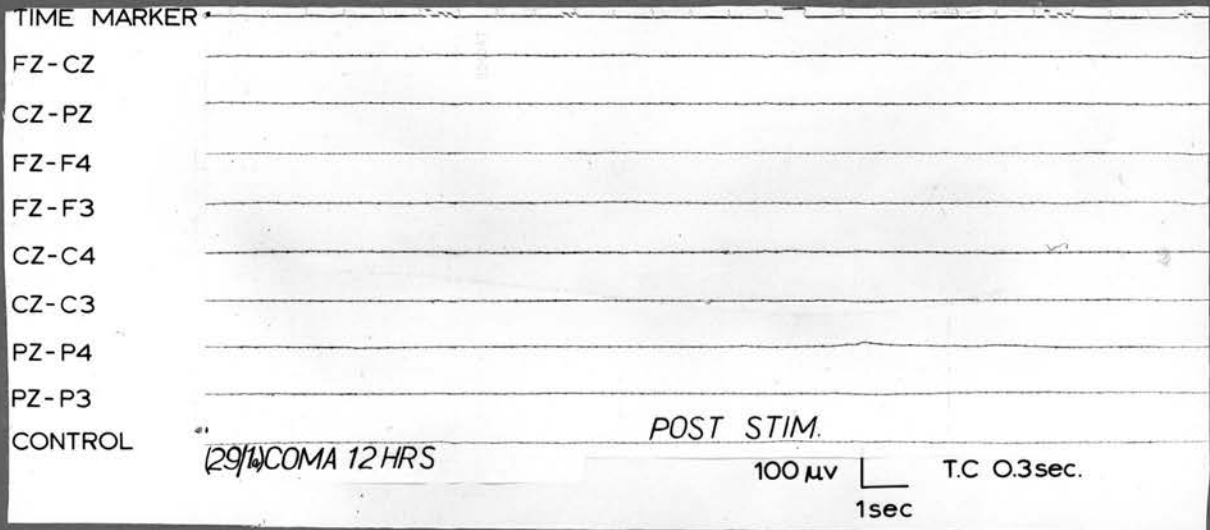


Figure 41:

Isoelectric EEG record approximately twelve hours after the patient took an overdose of barbitone. Blood barbitone level was 67.8 percent and rectal temperature 35.8°C .

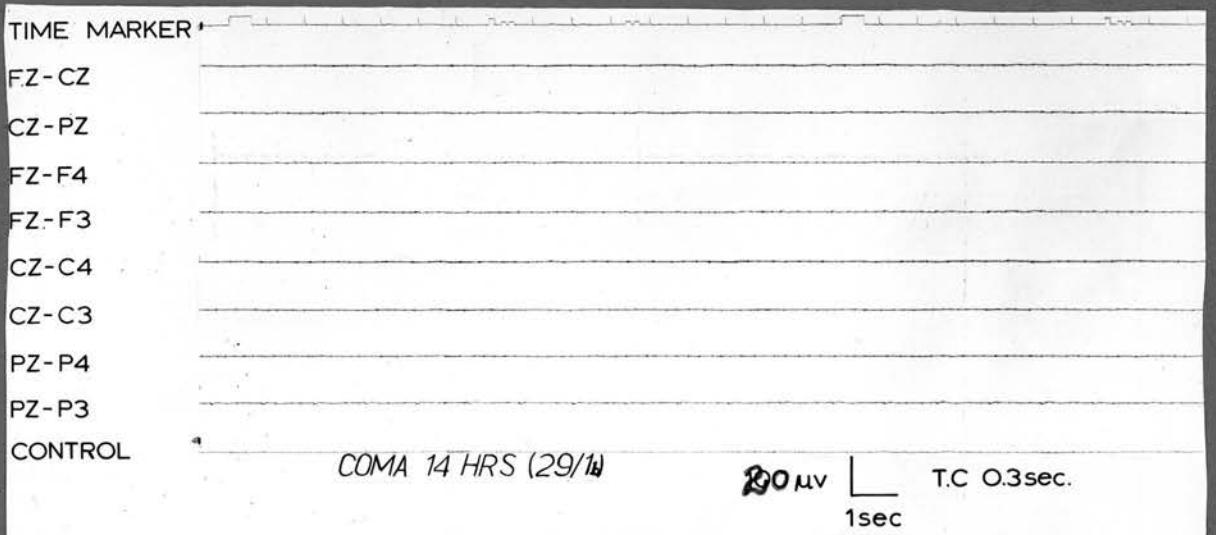


Figure 42:

After fourteen hours of coma EEG record remained isoelectric even on maximum amplification (20 micro-volts per cm.). Blood barbitone level was 70 mg. percent and rectal temperature 34.1°C .

EEG IN ACUTE BARBITONE POISONING
(Patient 14, Female, 64 years old).

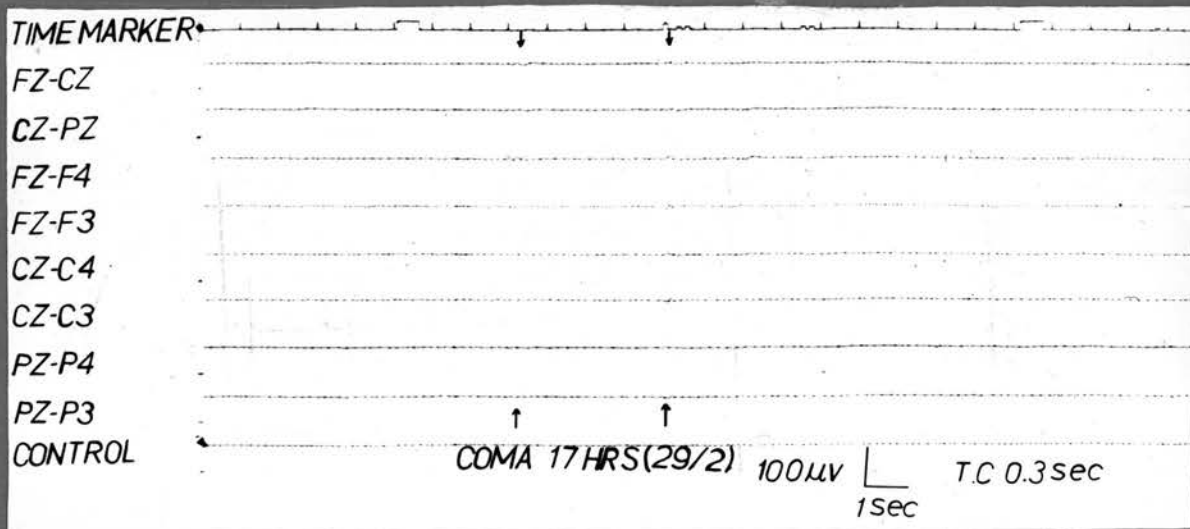


Figure 43:

After seventeen hours of coma record showed Grade VI EEG abnormality. It contained two isolated bursts of activity marked with the arrows. Blood barbitone level was 65 mg. percent.

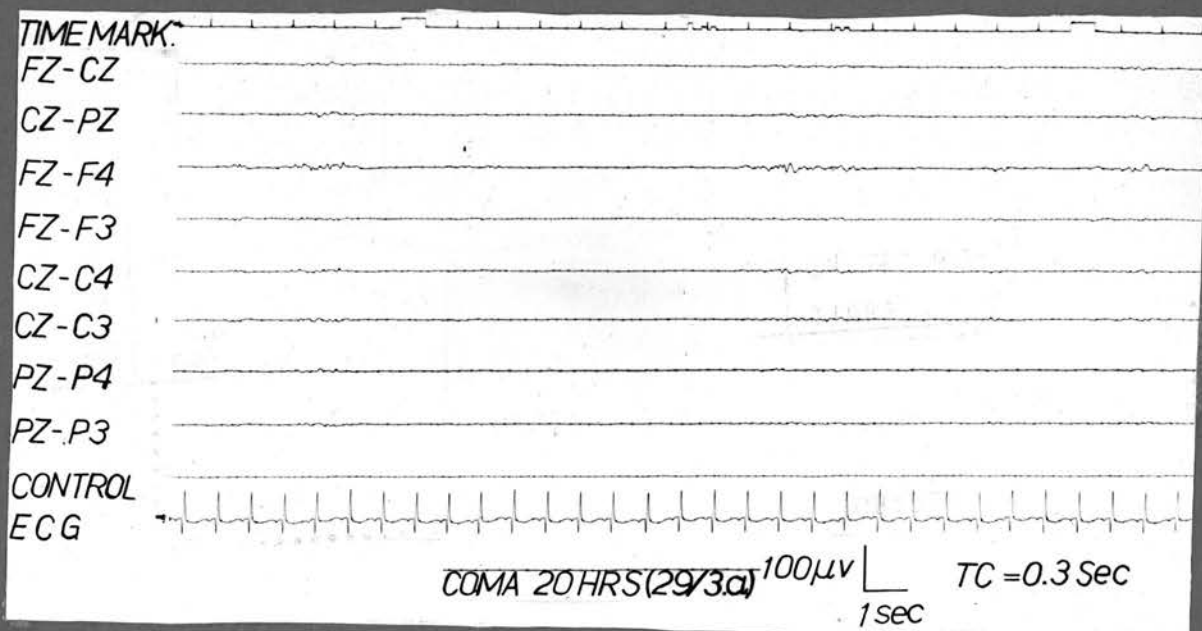


Figure 44:

After twenty hours of coma her tracings showed suppression burst activity (Grade V). Blood barbitone level was 65 mg. percent and rectal temperature 33.0°C.

EEG IN ACUTE BARBITONE POISONING.

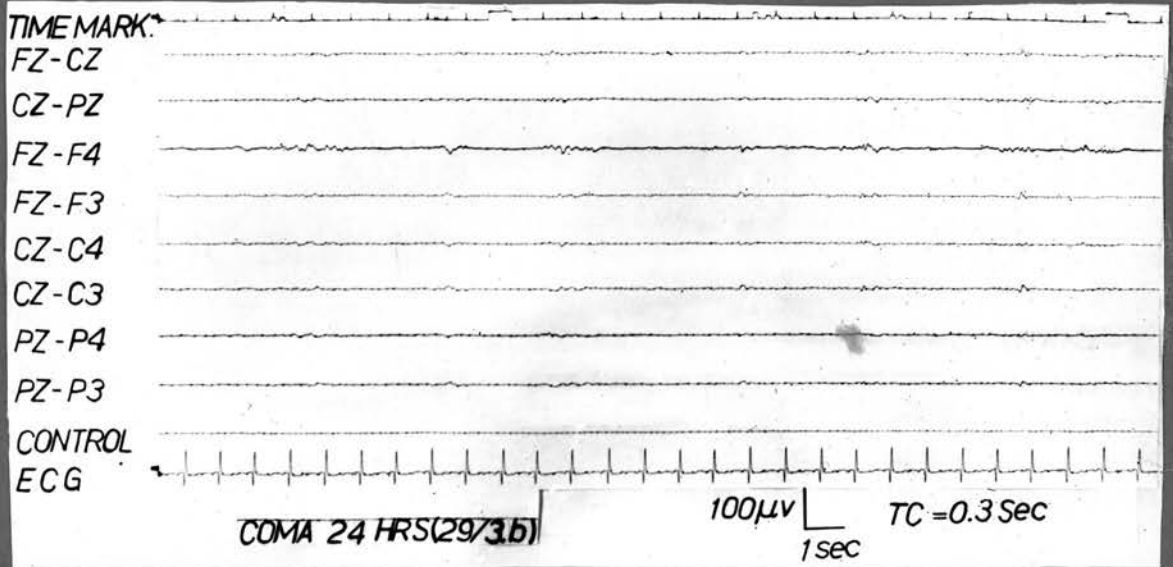


Figure 45:

After twenty four hours of coma no clinical response was observed on stimulation but her EEG record contained an increased amount of cerebral electrical activity (Grade V). Blood barbitone level was 62 mg. percent and rectal temperature 32.1°C.

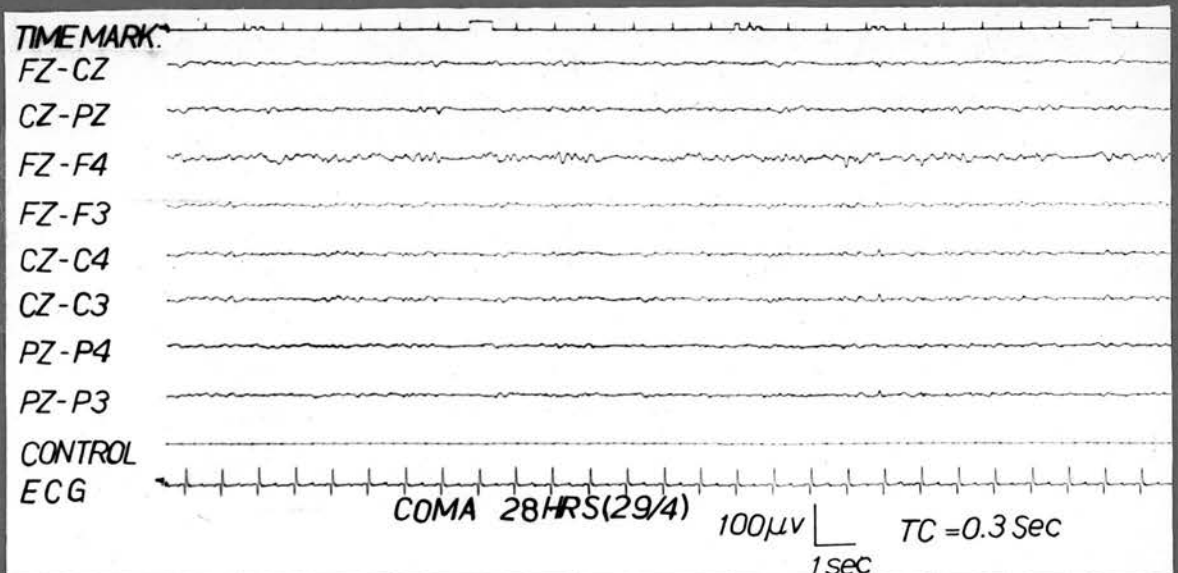


Figure 46:

Twenty eight hours after drug ingestion EEG tracings consisted of continuous 4-5 cps activity. Blood barbitone level was 55 mg. percent and rectal temperature 31.6°C. Clinically she was unresponsive to all stimuli.

activity increased both in quantity and amplitude. At the end of 32 hours her EEG tracings (Fig. 47) showed 2-3 cps activity more marked in the top three channels and low voltage 4-6 cps activity in other channels.

After 35 hours of coma her rectal temperature rose to 35.5°C and her serum barbitone level dropped to 42 mg.% but clinically she was still deeply unconscious and unresponsive to all stimuli. Her EEG record (Fig. 48) showed 4-6 cps activity with bursts of 2-3 cps activity. This showed further improvement over the next five hours and a record after 37 hours (Fig. 49) contained 2-5 cps in the top three channels and a dominant low voltage 4-6 cps in the remaining record. Cardiac irregularities were also seen. Her EEG record after 40 hours (Fig. 50) showed reduction in slow frequencies and contained 4-6 cps activity in the top three channels and low voltage 6-8 cps activity in the remainder of the record. Rectal temperature was 36.4°C and serum barbitone level 39 mg.%.

After remaining unconscious for 45 hours, she for the first time, responded clinically to painful stimulation. Four hours later examination of blood showed a serum barbitone level of 31 mg.% and rectal temperature of 37.2°C . After 54 hours of coma her EEG tracings (Fig. 51) before stimulation revealed 4-6 cps activity in the top three channels and low voltage 6-8 cps activity in the remaining five channels. After painful stimulation (rubbing of the sternum with the knuckles) the EEG record (Fig. 52) showed an increase in the voltage, 3-6 cps activity was seen in the top three channels and high voltage 5-8 cps in the remaining channels./

EEG IN ACUTE BARBITONE POISONING.

(Patient 14, Female, 64 year old).

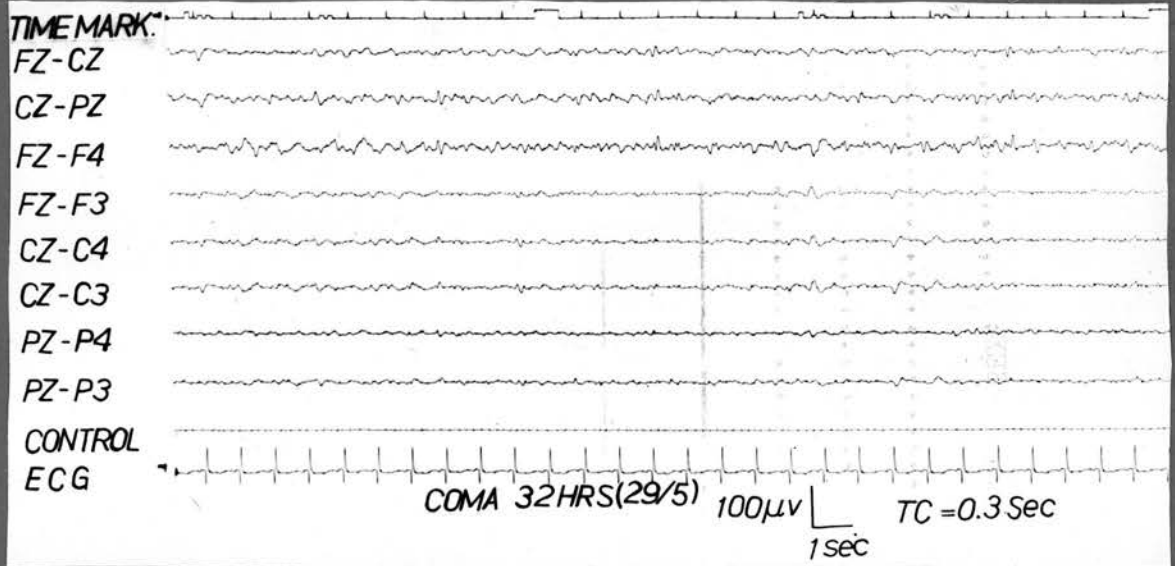


Figure 47:

After thirty two hours of coma, EEG record showed 2-3 cps activity in the top three channels and low voltage 4-6 cps activity in the lower five channels.

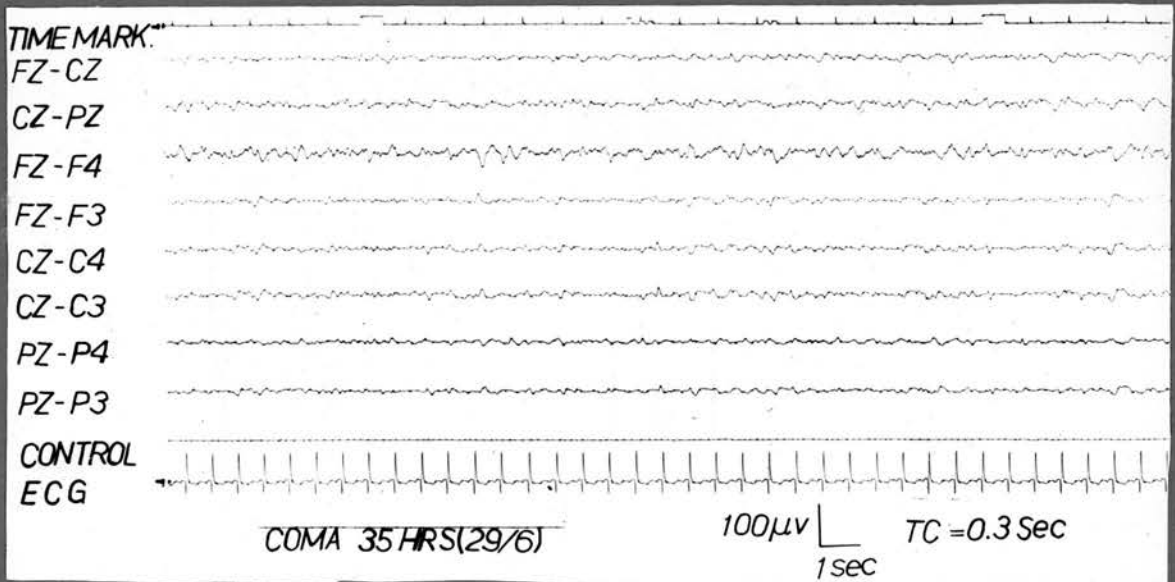


Figure 48:

Thirty five hours after lapsing into coma no clinical response was observed but her EEG record showed 4-6 cps activity with bursts of 2-3 cps activity. Blood barbitone level was 42 mg. percent and rectal temperature 35.5°C.

EEG IN ACUTE BARBITONE POISONING.
(Patient 14. Female. 64 years old).

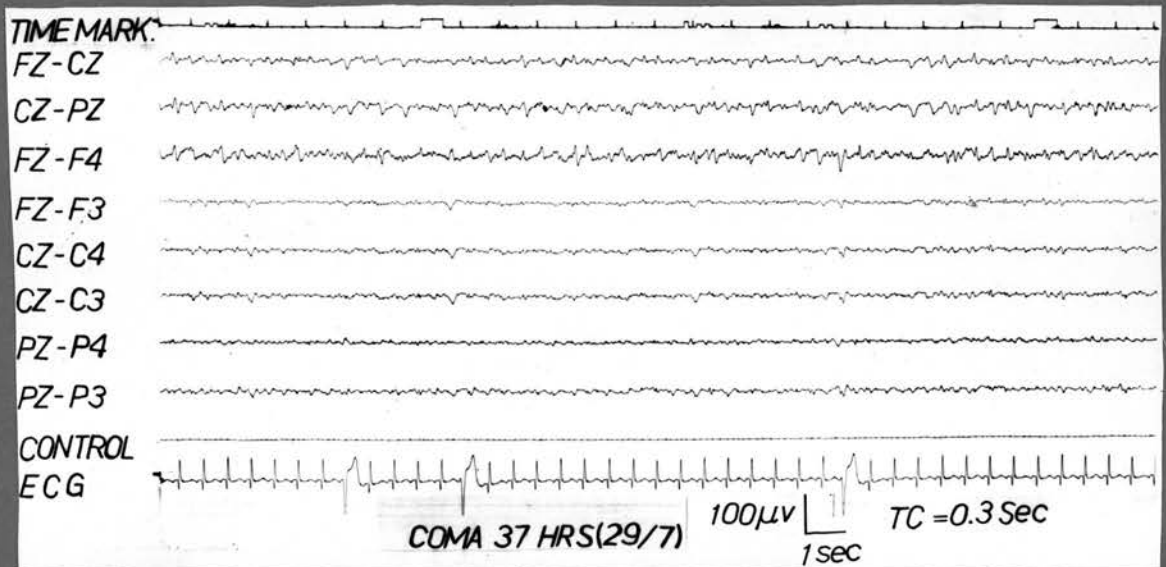


Figure 49:

After thirty seven hours her EEG record was dominated by 2-5 cps activity in the top three channels and low voltage 4-6 cps in the remaining record. Cardiac irregularities were also seen.

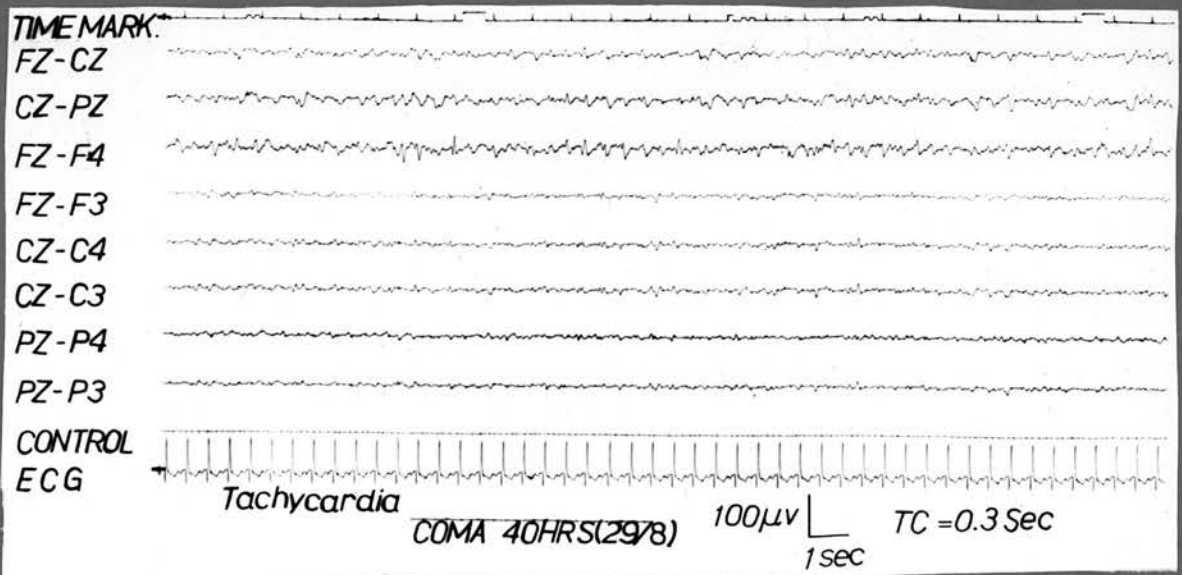


Figure 50:

Forty hours after lapsing into coma her EEG tracings showed 4-6 cps activity in the top three channels and low voltage 6-8 cps activity in the lower five channels. Blood barbitone level was 39 mg. percent and rectal temperature 36.4°C.

EEG IN ACUTE BARBITONE POISONING.
(Patient 14, Female, 64 years old).

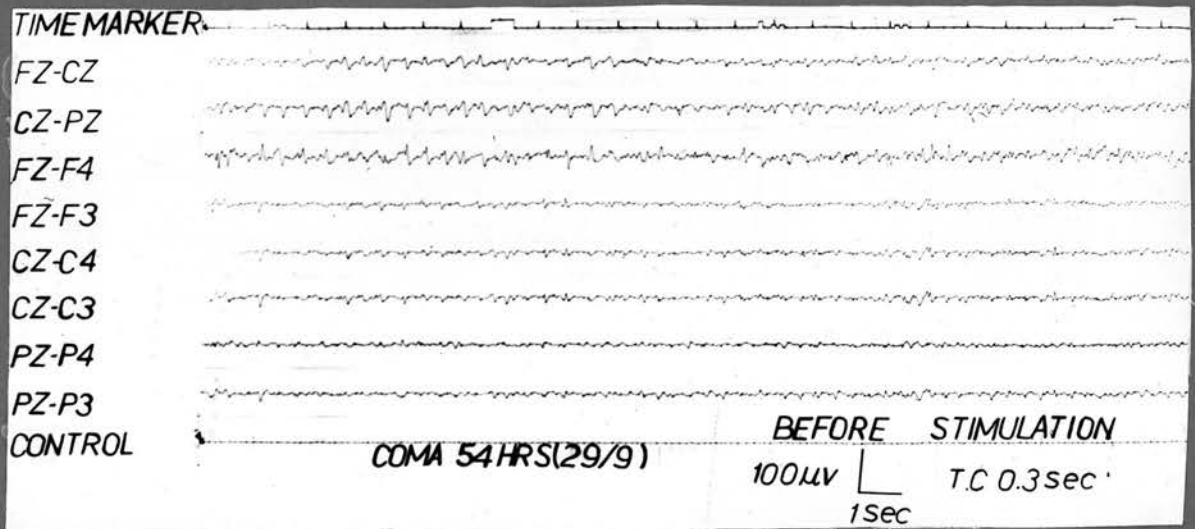


Figure 51:

After fifty four hours of coma a record before stimulation contained 4-6 cps activity in the top three channels and low voltage 6-8 cps activity in the remaining five channels. Blood barbitone level was 31 mg. percent and temperature 37.2°C.

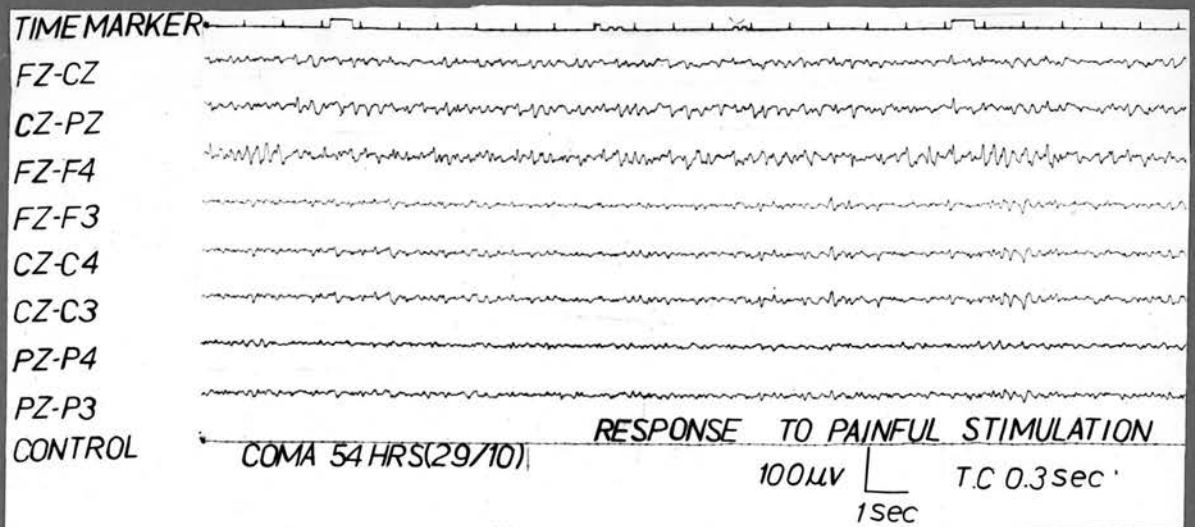


Figure 52:

After painful stimulation, the EEG tracings showed an increase in voltage 3-6 cps activity in the top three channels and high voltage 5-8 cps in the remaining five channels.

channels. In the EEG tracing taken after 56 hours of coma (Fig. 53) a spontaneous shift from slow to faster activity was observed, 4-7 cps activity with prominent 2-3 cps in the top three channels, gave way to faster frequencies at 6-9 cps. Figure 54 shows another spontaneous shift from faster frequencies to slower frequencies. Clinically she showed vigorous response to painful stimuli. Her rectal temperature was 37.2°C and serum barbitone level 28 mg.%.

After remaining unconscious for 59 hours she made appropriate response to vocal command but remained very drowsy. EEG monitoring was continued and 60 hours after ingestion of the drug her EEG tracings (Fig. 55) showed some activity at 5-7 cps mixed with 8-10 cps activity in the top three channels and more generalized low voltage 6-8 cps activity with some 2-4 cps activity.

Sixty eight hours after drug ingestion (nine hours post-coma), she was very drowsy and on being left undisturbed, appeared asleep. Her EEG (Fig. 56) consisted of dominant activity at 4-8 cps mixed with which was some 3-5 cps activity. She remained very drowsy for the next few hours. Her EEG after 73 hours (Fig. 57) showed a dominant activity of 7-8 cps with some 3-5 cps. Muscle artefact was also visible. Her serum barbitone level was 21.6 mg.% and temperature 36.6°C . She continued to improve and her EEG record after 91 hours (31 hours post-coma) was recorded while the patient was awake (Fig. 58). It showed eye blinks. Dominant activity was 7-13 cps with occasional bursts of 2-4 cps activity. Her serum barbitone level was 10.8 mg.% after 107.50 hours.

One/

EEG IN ACUTE BARBITONE POISONING.
(Patient 14, Female, 64 years old).

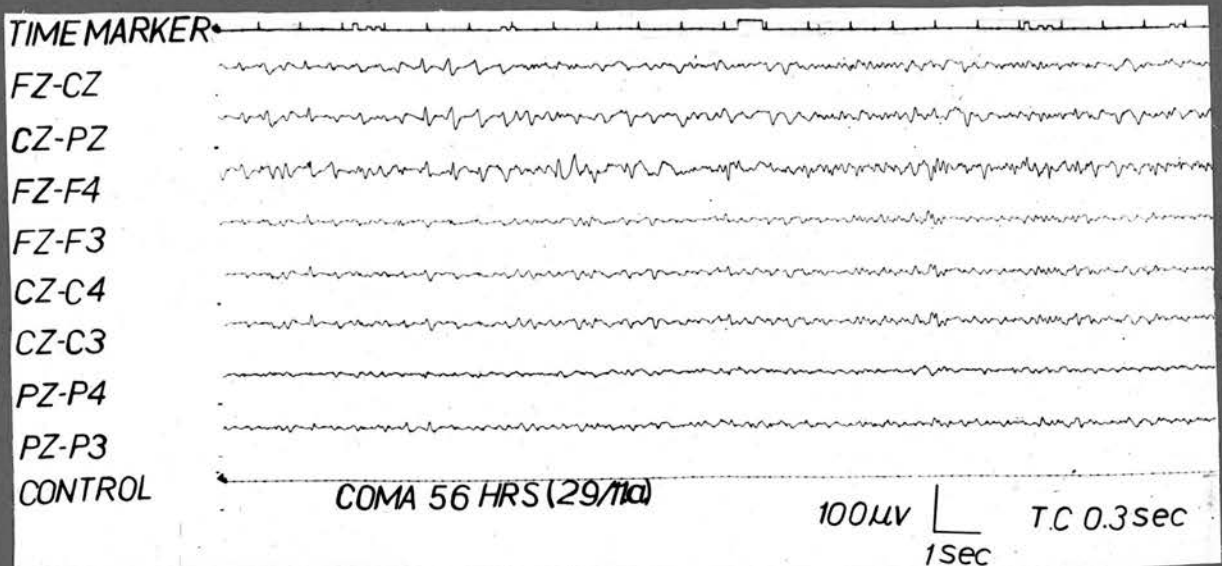


Figure 53:

After fifty six hours of coma EEG record contained a spontaneous shift. Slow wave activity at 4-7 cps with predominant 2-3 cps in the top three channels gave way to faster frequencies at 6-9 cps.

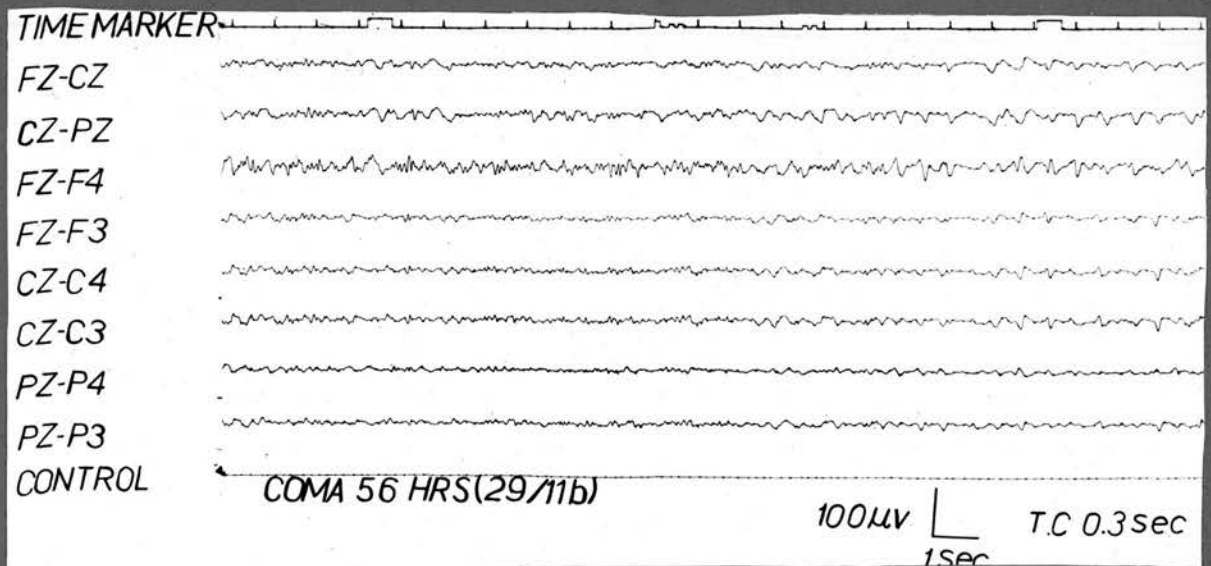


Figure 54:

Another example of a spontaneous shift. The dominant activity at 6-9 cps with some 3-4 cps activity gives way to slow wave activity at 2-4 cps. Blood barbitone level was 28 mg. percent and rectal temperature 37.2°C.

EEG IN ACUTE BARBITONE POISONING.

(Patient 14, Female, 64 years old).

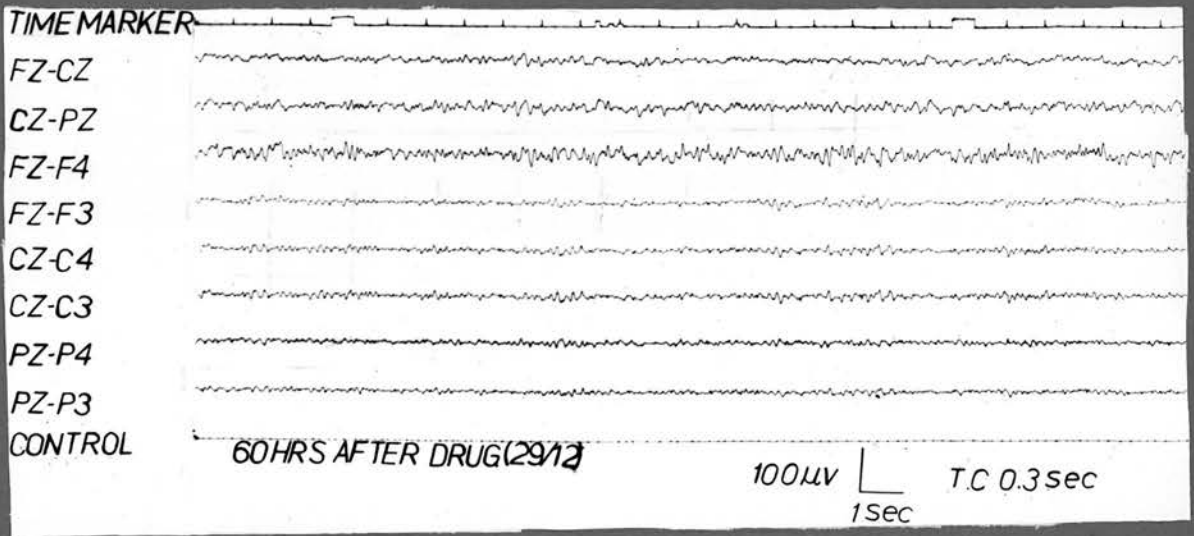


Figure 55:

Sixty hours after drug ingestion (one hour post coma) EEG tracings showed some activity at 5-7 cps mixed with 8-10 cps activity in the top three channels and low voltage 6-8 cps activity with some 2-4 cps activity in the lower five channels.

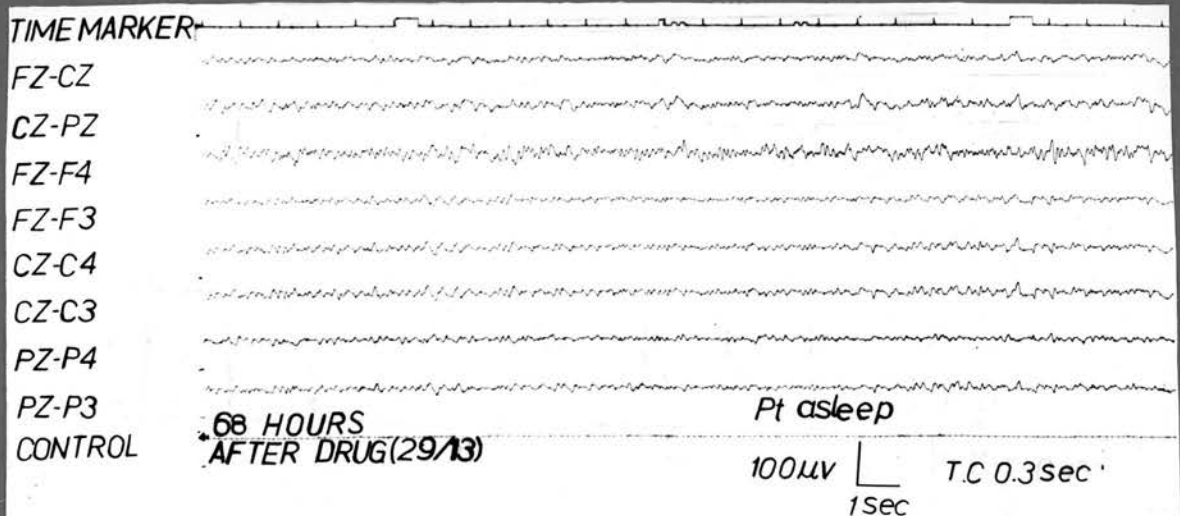


Figure 56:

Nine hours post coma, she appeared asleep. Her EEG tracings contained dominant activity at 4-8 cps mixed with which was some 3-5 cps activity.

EEG IN ACUTE BARBITONE POISONING
(Patient 14, Female, 64 years old).

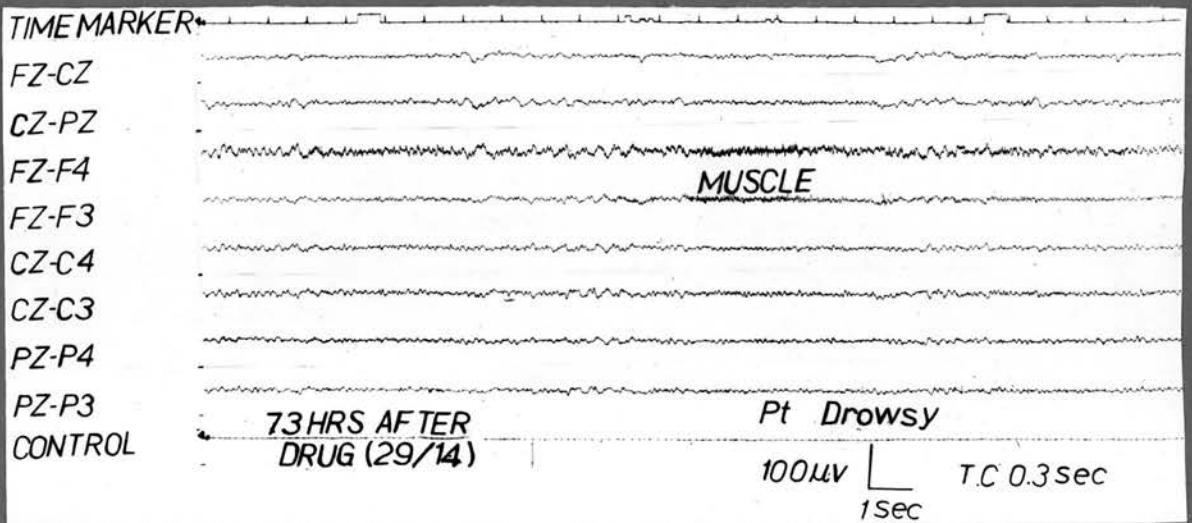


Figure 57:

After seventy three hours (14 hours post coma) her record showed a dominant activity of 7-8 cps with some 3-5 cps. Muscle artefact was present. Blood barbitone level was 21.6 mg. percent and temperature 36.6°C.

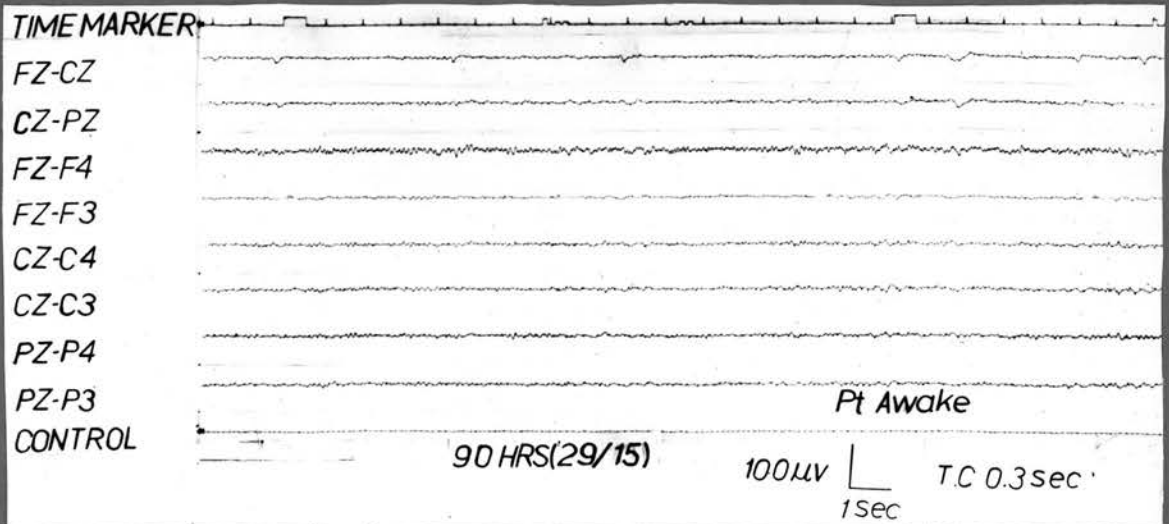


Figure 58:

Thirty one hours post coma while the patient was awake her EEG contained dominant activity at 7-13 cps with occasional bursts of 2-4 cps activity. It showed eye blinks.

One hundred and thirty hours after ingestion of the drug the EEG record (Fig. 59) revealed a generalised flatness with prominent blinks. The background activity consisted of low voltage 7-10 cps which was blocked by eye closure. Her serum barbitone level was 9.5 mg.%. On the 8th day of her admission her EEG record (Fig. 60) showed generalised 8-10 cps activity.

On the 5th night of her admission she was reported to have "slept very little" by the night staff. However, during the day she was quite comfortable. The next night (3rd post-coma night) she was reported to be "awake most of the night, seems to be very confused at times" and during the day she developed some withdrawal symptoms. She became confused, disorientated and paranoid for which she received thioridazine 50 mg. six hourly orally. For her insomnia she was prescribed 10 mg. nitrazepam on the 7th hospital night, 5 mg. on the 8th and 10 mg. on the 9th night. Her psychometric testing showed no deficit and she was discharged home on the 9th hospital day.

Her EEG record after one month (Fig. 61) and psychological tests were normal. EEG and psychological tests were repeated at intervals of three, six and nine months but they were normal.

CASE HISTORY No. 4 (59/41/J.M.)

A man, aged 56, was admitted to the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh at 08.00 hours on the 15th June, 1968, after having been found unconscious. He had been last seen by his wife at 22.00 hours on 14th June. Mandrax had been prescribed/

EEG IN ACUTE BARBITONE POISONING
(Patient 14, Female, 64 years old).

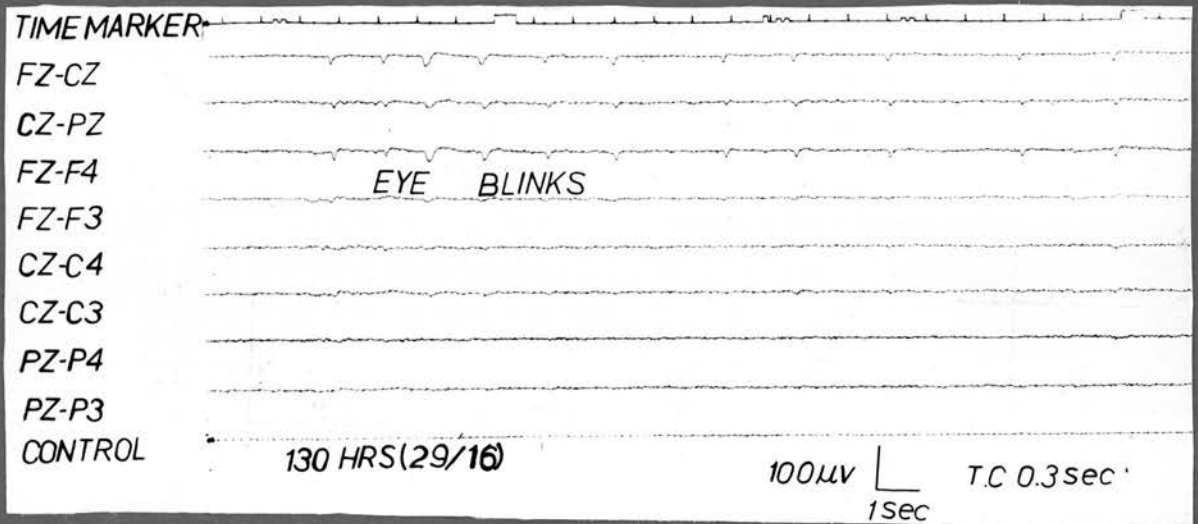


Figure 59:

A record 130 hours after the ingestion of drug (71 hours post coma) revealed a generalised flatness with prominent blinks. The background activity consisted of low voltage 7-10 cps and was blocked by eye closure. Blood barbitone level was 9.5 mg. percent.

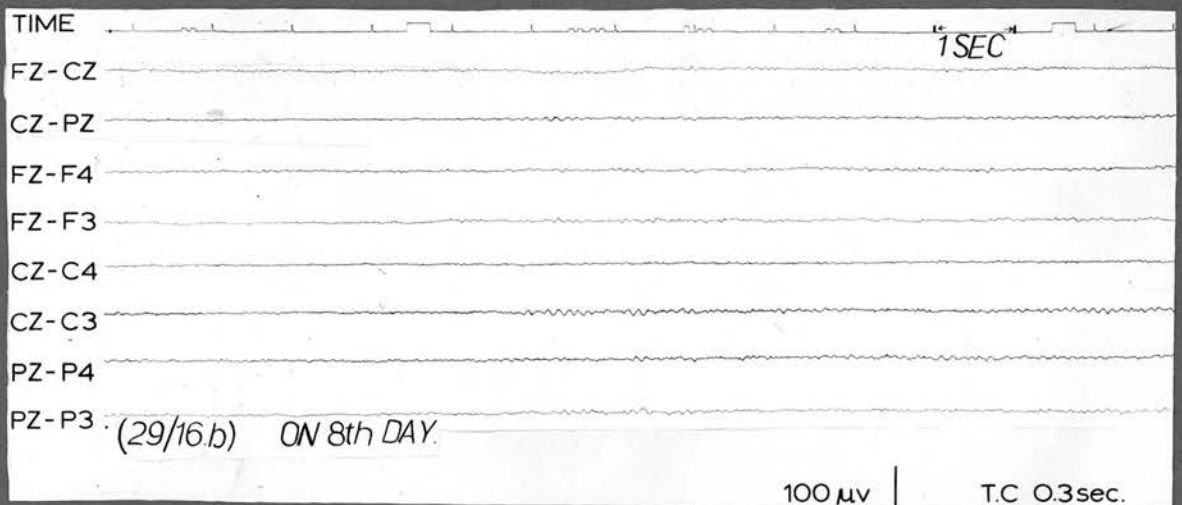
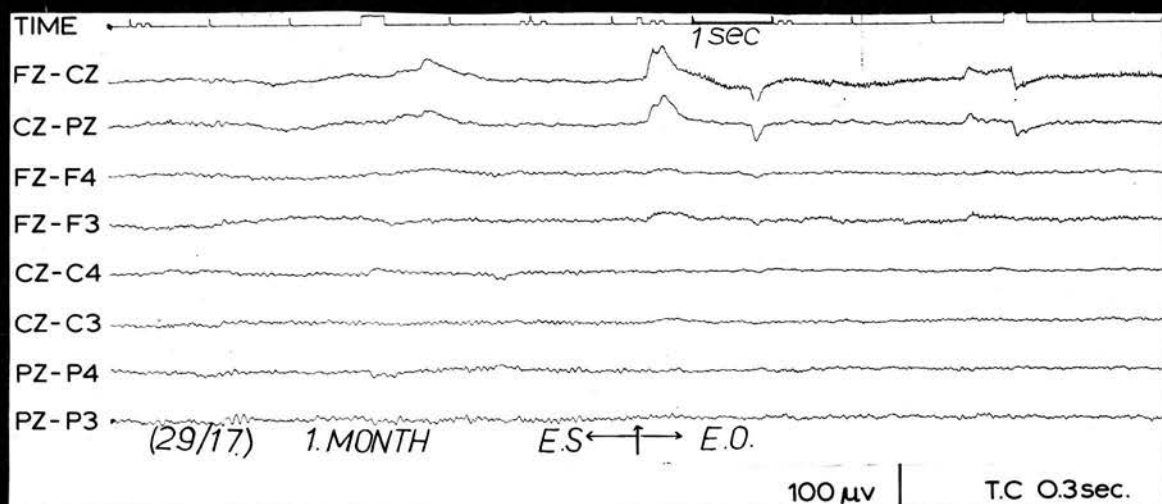


Figure 60:

On her 8th hospital day the EEG record showed generalised 8-10 cps activity.



prescribed for his insomnia and was available to him. Consequently Mandrax overdose was considered but he had no physical signs considered diagnostic.

During the previous three years he had been crippled owing to two attacks of myocardial infarction, a carcinoma of the prostate under treatment with stilboestral, a pathological fracture of the right femur, and trigeminal neuralgia requiring tarsorrhaphy after seventh nerve section.

Course in the Hospital:-

On admission he was deeply unconscious and totally unresponsive to all stimuli, including rubbing of the sternum with the knuckles and pinching of the earlobes. His pupils were small and fixed. Cough, corneal and gag reflexes were absent. Plantar reflexes were extensor and the muscles flaccid. Bowel sounds were present. Pulse was 80 per minute, regular, poor in volume, systolic blood pressure 60 mm.Hg. and respiration Cheyne-Stokes type. Otherwise there were no localizing signs. An endotracheal tube was passed and intensive supportive therapy instituted. A blood sample tested for drugs revealed very high methaqualone level of 9.0 mg.%. Continuous EEG monitoring was started and his record (Fig. 62) showed isoelectric tracings which showed no change even on stimulation (Grade VII). EEG recordings made with maximum gains (20 microvolts per cm.) was still isoelectric (Fig. 63). Over the next 12 hours his condition deteriorated. His bowel sounds disappeared and he developed pneumonia. His rectal temperature was 37.8°C and blood methaqualone level 12.0 mg.%. His EEG record (Fig. 64) remained isoelectric (Grade VII).

Twenty nine hours after the ingestion of the drug he was still deeply unconscious making no clinical response to any/

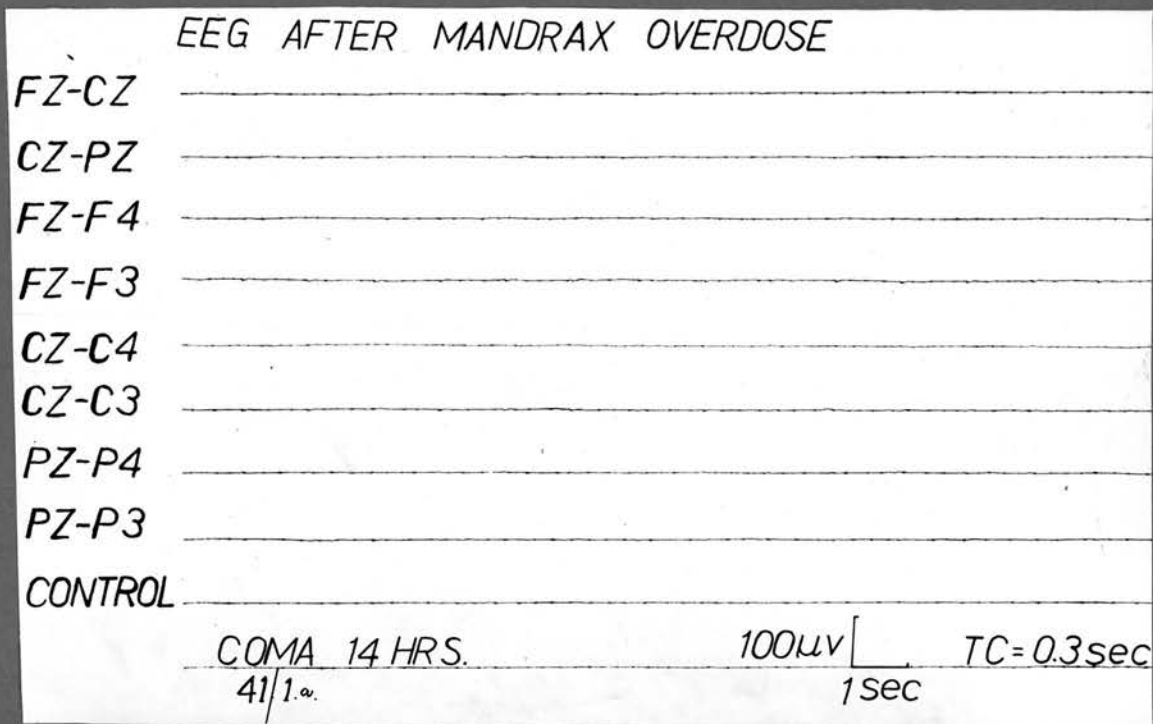


Figure 62:

Fourteen hours after drug ingestion his EEG record (on average gain - 100 µv. per cm) revealed isoelectric tracings (Grade VII). His blood methaqualone level was 9.0 mg. percent.

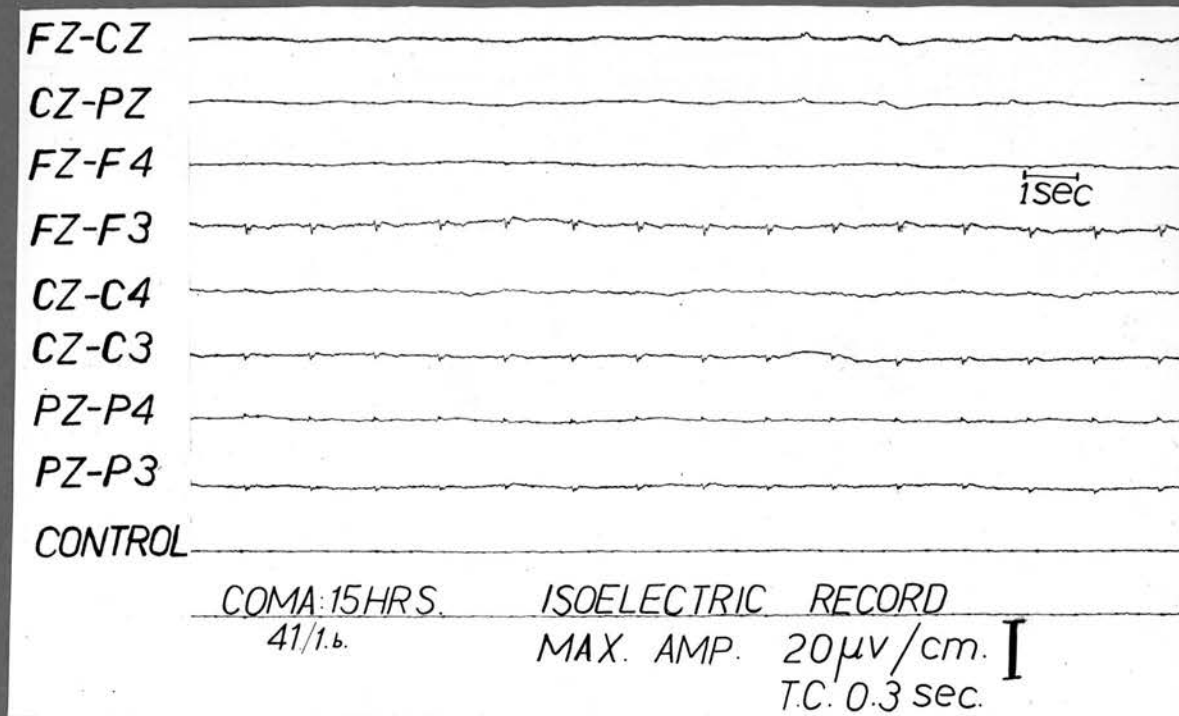


Figure 63:

EEG recording made with maximum amplification (20 µv/cm) was also isoelectric. Three waves seen in the top two channels are artefact as they do not appear in other channels in spite of electrodes F_Z, C_Z and P_Z being common to other channels.

EEG IN ACUTE MANDRAX POISONING

Patient 59 - Male 56 years old.

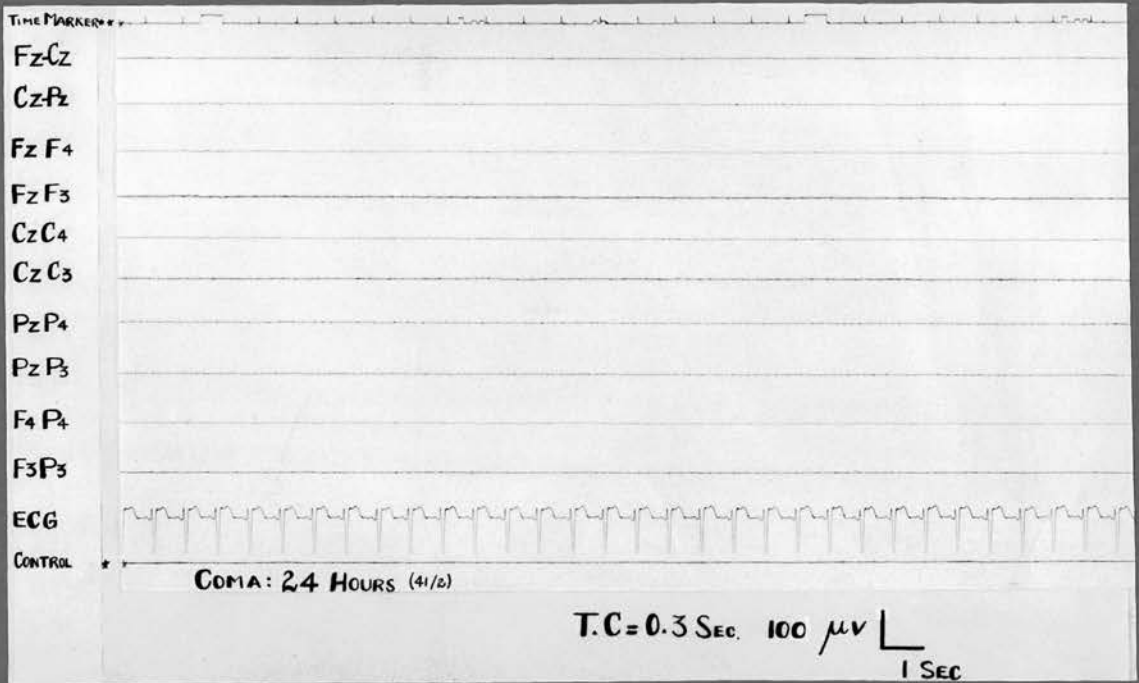


Figure 64:

Twenty hours after lapsing into coma his EEG tracings showed no sign of cerebral electrical activity. His rectal temperature was 37.8°C and blood methaqualone level 12.0 mg. percent.

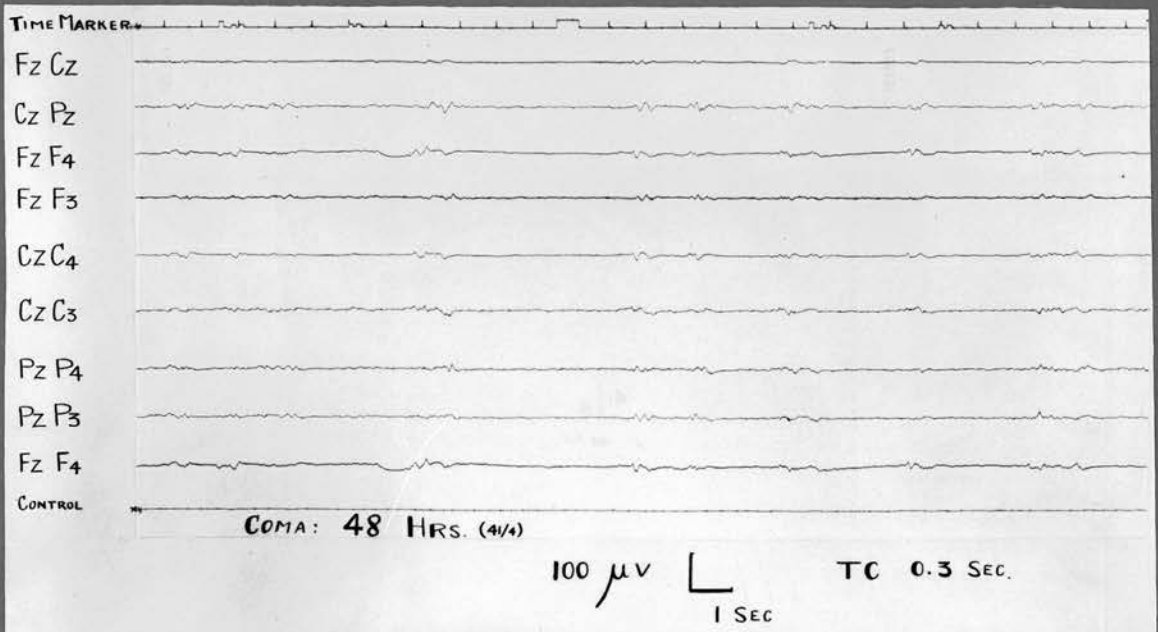


Figure 65:

After forty eight hours of coma, his EEG record revealed Grade V abnormality. (suppression burst activity). His rectal temperature was 37.8°C and blood methaqualone level was 9.6 mg. percent.

any stimuli, but his EEG record first showed a burst of activity in response to stimulation of sternum with knuckles. His blood methaqualone was 12.3 mg.% and rose to 12.9 mg.% at the end of 30 hours. After 33 hours of coma EEG record showed spontaneous isolated bursts of activity. Thereafter his EEG record continued to show increased activity but he gave no clinical response to painful stimuli. His methaqualone level was reported to be 12.9 mg.% at thirty hours after the drug ingestion.

After 48 hours there was no change in his clinical condition but his EEG record (Fig. 65) showed suppression burst features in the EEG (Grade V) with 1-3 seconds of activity alternating with 10-15 seconds of electrical silence. This activity could be increased by sternal stimuli. The blood methaqualone level was 9.6 mg.% and the rectal temperature 37.8°C. His clinical condition remained unchanged for 64 hours after drug ingestion, but his EEG (Fig. 66) now showed continuous delta activity without any intervening flat areas (Grade IV). Sixty six hours after the drug, he was responding minimally to maximum painful stimulation. His temperature was 39.1°C.

After sixty nine hours of coma there was a sudden deterioration in the patient's condition. There was profuse sweating, trembling of the whole body, restlessness and tachycardia and soon after this he once again was deeply comatose and unresponsive to stimuli. This deterioration in his clinical state was preceded by change in his EEG which showed the return of silent areas. One hour later the EEG record showed suppression burst activity, a record/

EEG IN ACUTE MANDRAX POISONING

Patient 59 - Male 56 years old.

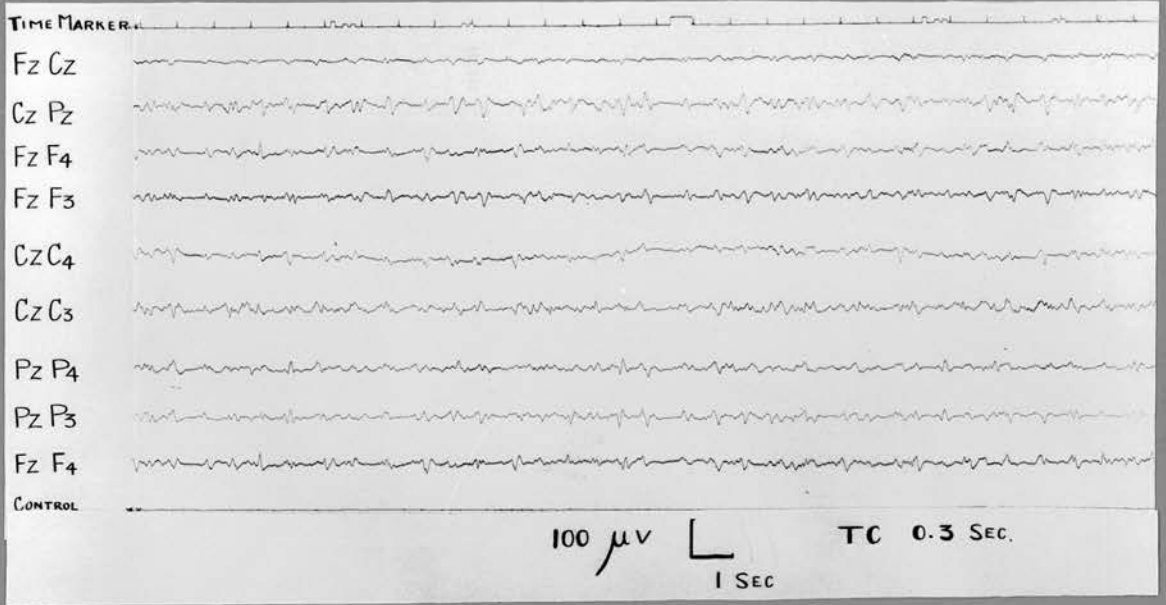


Figure 66:-

After sixty hours of coma his EEG tracings contained a mixture of low and high voltage continuous delta activity. His rectal temperature was 39.1°C.

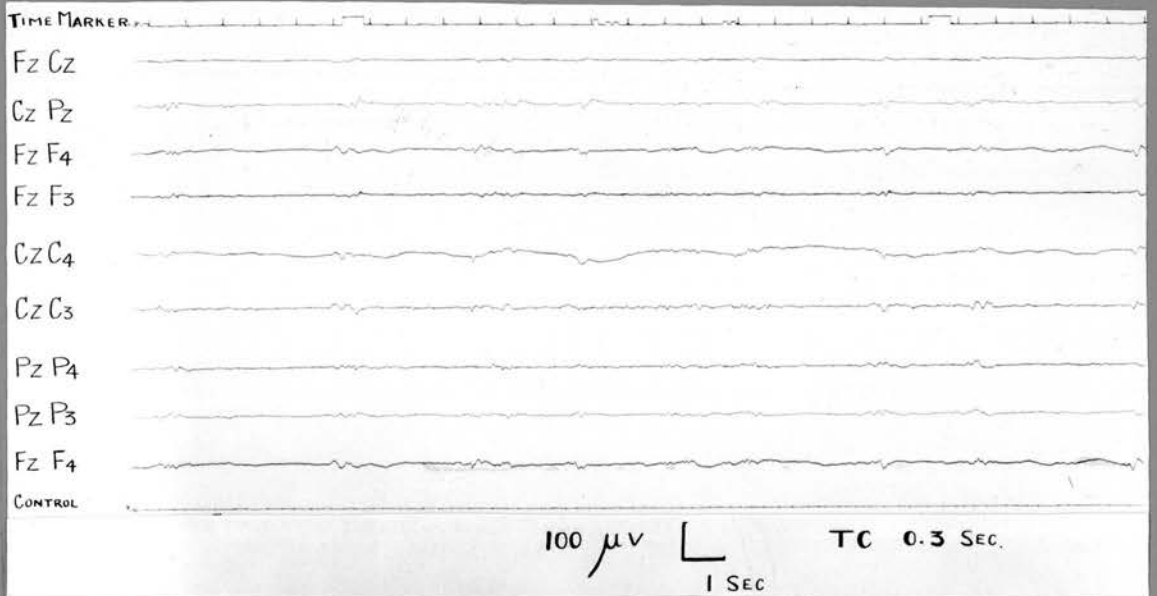


Figure 67:

Seventy hours after lapsing into coma his EEG record showed return of suppression burst activity (Grade V), a record similar to that seen after only 48 hours of coma (Figure 65). His rectal temperature was 39.3°C and blood methaqualone 8.1 mg. percent.

record similar to that seen after only 48 hours of coma (Fig. 67). His temperature was now 39.3°C and blood methaqualone level 8.1 mg. percent.

However his condition again improved during the next twelve hours and he reacted to the presence of the endotracheal tube which therefore was removed. His temperature came down to 38.8°C from 40.3°C after 81 hours. The blood methaqualone concentration was 6.2 mg.%. His EEG also showed improvement. An ECG taken at this time revealed left bundle branch block but this was reported to have been present for the previous 4 months since he had had myocardial infarction. Thereafter he continued to make satisfactory progress and after 92.50 hours he was responding moderately to sternal stimuli. His rectal temperature was 38.2°C and the blood methaqualone level had dropped to 4.7 mg.%.

After remaining in coma for 106 hours he made appropriate response to vocal command, but remained very frail and confused. His methaqualone level was 2.5 mg.% and temperature 37.5°C . On the 21st June, (7th hospital day) he rapidly developed left ventricular fibrillation and died within a few hours despite active measures. The post mortem showed a recent myocardial infarction which was accepted as the cause of death. It was suggested that as Mandrax is liable to cause disturbances of the electrocardiogram, and of myocardial enzymes, it may have accelerated his death. However, very little Mandrax was present in the blood (0.8 mg.%), when he died.

CASE HISTORY No.5 (72/110/E.S.)

A 49 year old female was admitted to the Regional Poisoning/

Poisoning Treatment Centre on 21st March, 1969 after having taken a large quantity of Mandrax tablets 12 hours prior to hospitalisation. She had been attending the psychiatric Out-Patient Clinic and had been prescribed Mandrax by her family doctor.

Course in the Hospital:-

On admission she was deeply unconscious, responding minimally to maximal stimulation. Her pulse was 84 per minute, regular and of good volume and blood pressure 80/40 mm.Hg. The reflexes were all intact and normal and muscle tone was normal. Stomach wash-out was not carried out in view of the time lapse since she took the tablets. It is worthy of note that she lacked all the diagnostic clinical signs of Mandrax poisoning, such as increased muscle tone and hyper-reflexia. Blood examination revealed a methaqualone level of 4.1 mg. percent.

Her electroencephalographic tracings (Fig.68) showed bursts of 2-4 cps activity with superimposed 4-6 cps activity. Over the next two hours deterioration and contained suppression burst activity. Clinically the patient was deeply unconscious and did not respond to sternal stimulation. Her bowel sounds were absent. The respiratory minute volume was 5 litres.

After 30, hours of coma her respiratory minute volume was 5 litres and her EEG record showed suppression burst activity (Fig. 69). Her blood methaqualone level was 8.6 mg.%. After thirty four hours of coma she was deeply unconscious, hypotonic and areflexic but had faint bowel sounds. Her EEG record remained unchanged. Her methaqualone blood level was 9.3 mg.%.

Her/

EEG IN ACUTE MANDRAX POISONING.
Patient 72 - Female, 49 years Old.

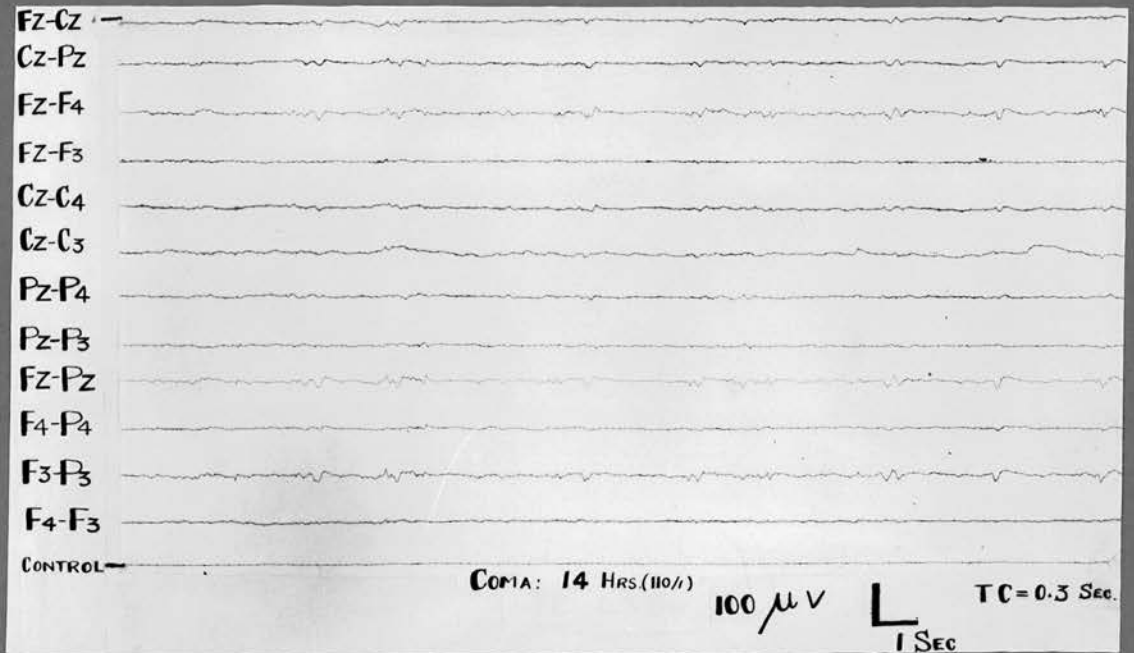


Figure 68:

Fourteen hours after ingestion of Mandrax her EEG record revealed Grade V EEG abnormality. It contained bursts of 2-4 cps activity with superimposed 4-6 cps activity. Her blood methaqualone was 4.1 mg. percent.

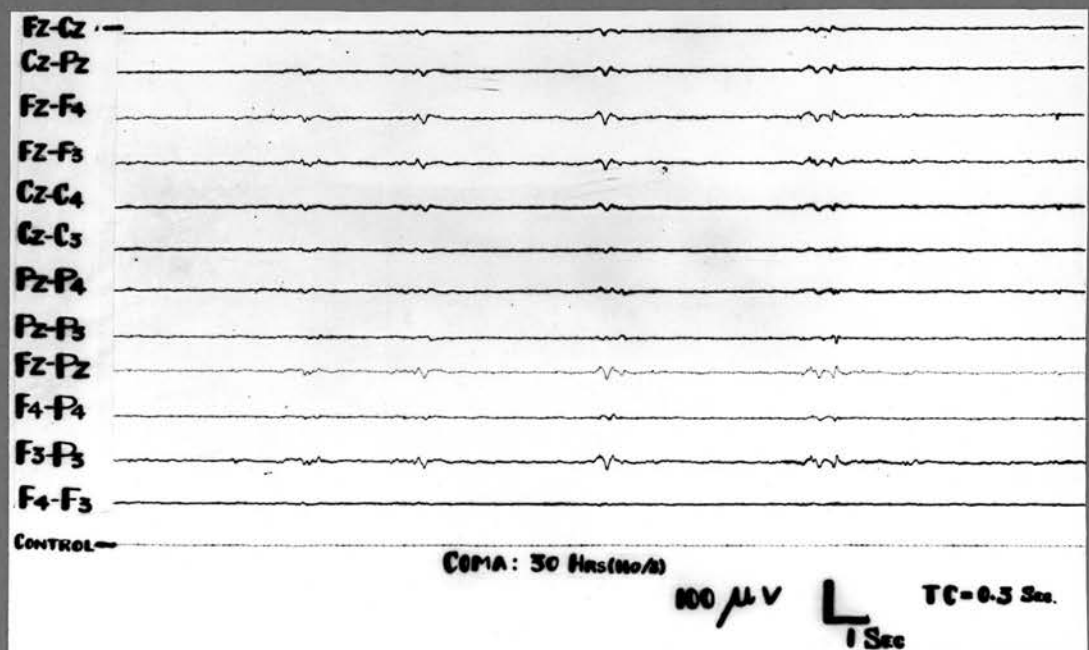


Figure 69:

After thirty hours of coma her EEG tracings showed Grade V EEG abnormality (suppression burst activity). Blood methaqualone level was 8.6 mg. percent.

Her EEG tracings after 43 hours (Fig. 70) showed improvement and contained dominant activity at 2-6 cps. Blood methaqualone level was 11.7 mg.%. Clinically the patient's condition remained unchanged and her blood methaqualone level after 47 hours was 10.2 mg.%. Her EEG continued to improve and after 56 hours (Fig. 71) it contained slow activity at 1-3 cps with some 2-6 cps. Superimposed on the slow waves were 6-8 cps faster frequencies. Her blood methaqualone level was 7.8 mg.%.

After 58 hours, she was still deeply unconscious, hypotonic and areflexic. Her methaqualone level was 7.8 mg.%. She was intubated and gastric lavage performed. Four hours later her methaqualone level rose to 10.2 mg.%. Electrically she continued to improve and EEG tracings showed 2-6 cps activity with some superimposed 6-8 cps activity.

After 69 hours of coma she responded minimally to sternal stimulation. Three hours later her EEG record (Fig. 72) contained high voltage 3-6 cps activity mixed with which was some low voltage activity at 6-9 cps. She continued to improve and the EEG tracings after 96 hours (Fig. 73) showed an increase in voltage and frequency. She regained consciousness after 105 hours of coma but 110 hours after ingestion of the drug her arms and legs were twitching and she became restless. Her EEG record (Fig. 74) showed a mixture of slow waves at 3-4 cps and faster activity at 6-10 cps.

She/

EEG IN ACUTE MANDRAX POISONING.

Patient 72 - Female - 49 years old.

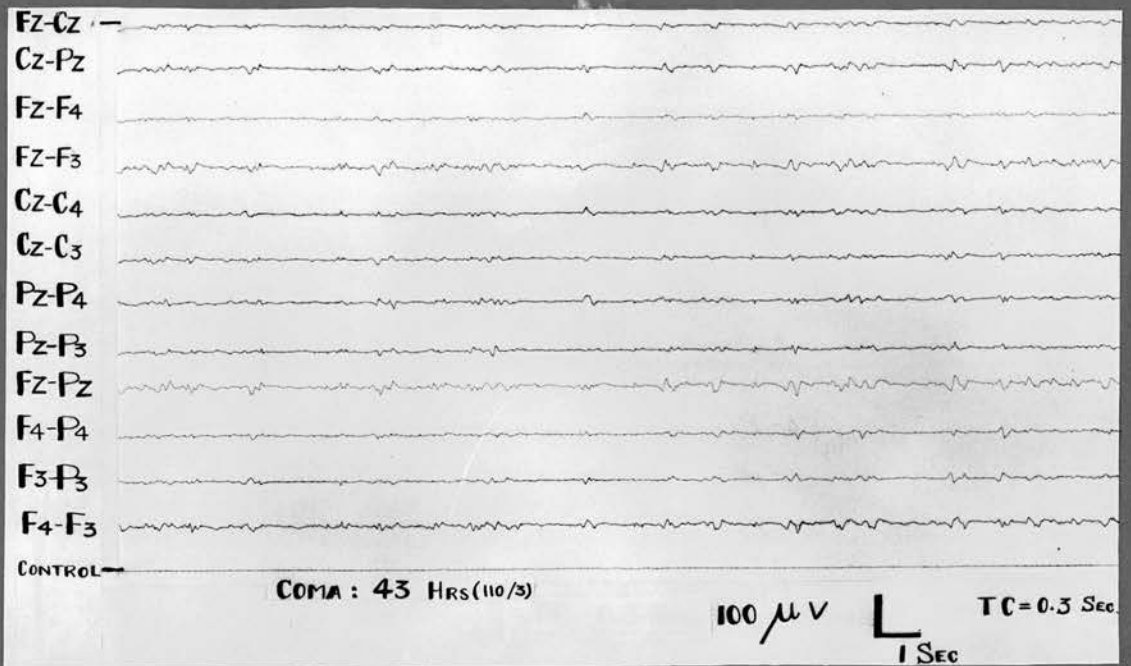


Figure 70:

Forty three hours after lapsing into coma her EEG record contained bursts of 2-6 cps activity separated by areas of less activity. Blood methaqualone level was 11.7 mg.percent.

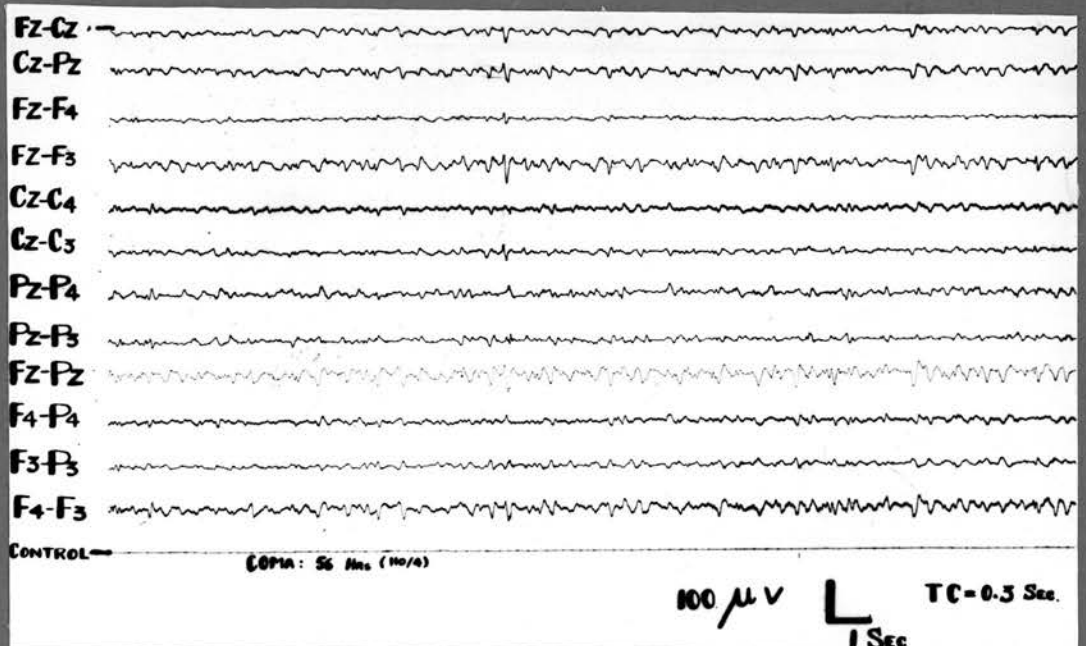


Figure 71:

After fifty six hours of coma her EEG revealed slow wave activity at 1-3 cps mixed with which was some 2-6 cps activity. Superimposed on the slow wave activity were 6-8 cps faster frequencies. Blood methaqualone level was 7.8 mg. percent.

EEG IN ACUTE MANDRAX POISONING.
Patient 72 - Female, 49 years old.

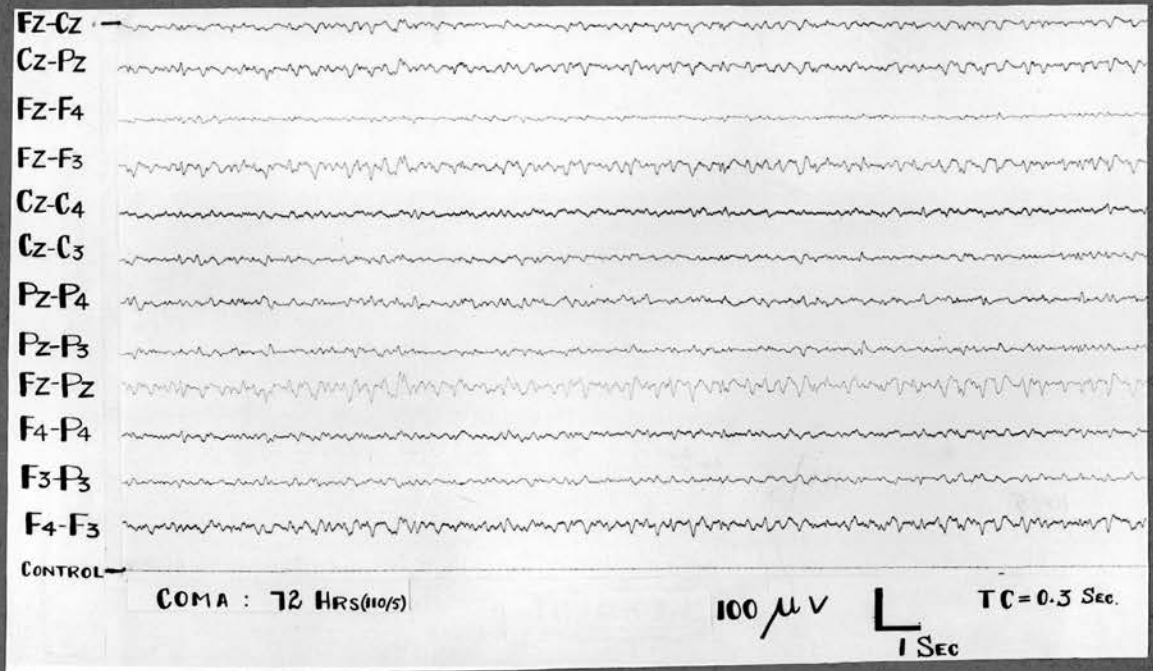


Figure 72:

After seventy two hours of coma her EEG consisted of a mixture of 2-3 cps slow waves and 6-0 cps faster activity. Blood methaqualone was 7.4 mg. percent.

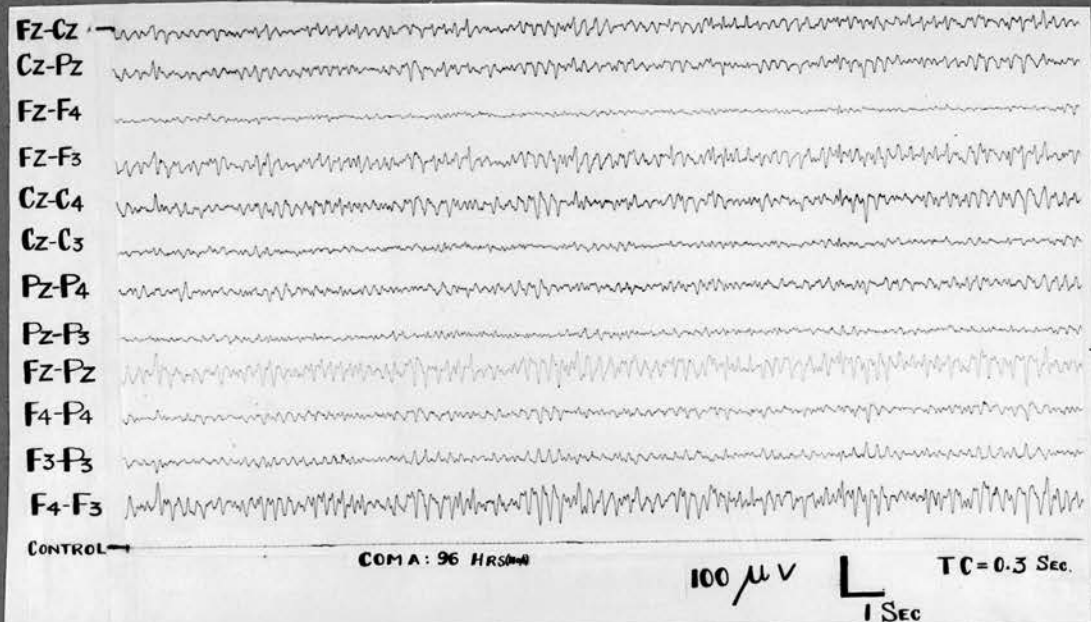


Figure 73:

EEG tracings after ninety six hours of coma showed an increased voltage and frequency namely, high voltage 3-6 cps activity mixed with which was some low voltage 6-9 cps activity. Blood methaqualone level was 4.5 mg. percent.

EEG IN ACUTE MANDRAX POISONING
Patient 72, Female, 49 years old.

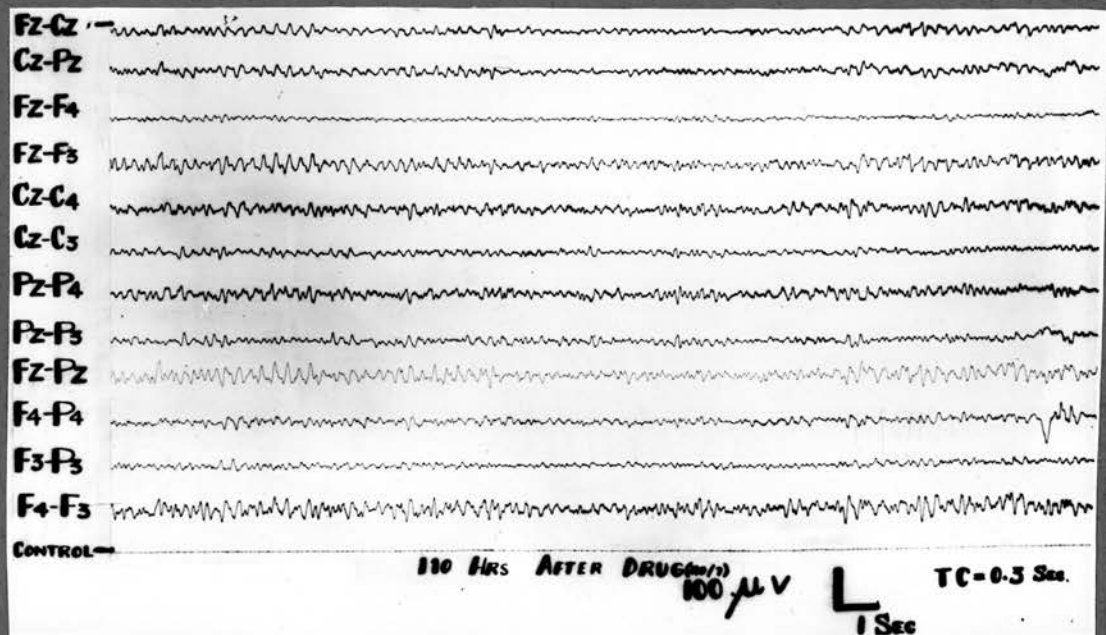


Figure 74:

One hundred and ten hours after ingestion of the drug her EEG record showed a mixture of slow waves at 3-4 cps and 6-10 cps activity.

She made a full clinical recovery and was seen by the Consultant Psychiatrist who transferred her to the North Wing of the Royal Edinburgh Hospital for psychiatric In-Patient care. The further recovery of this patient is discussed in Project No. 3 (Patient No. 1).

CASE HISTORY No. 6 (104/57/C.T.)

A 41 year old male was admitted to the Regional Poisoning Treatment Centre, Edinburgh Royal Infirmary, at 04.30 hours on 2nd December, 1968, after having taken 50 tablets (2500 mg.) of orphenadrine hydrochloride (Disipal) and 20 tablets (500 mg.) of promazine hydrochloride (Sparine) about three quarters of an hour previously. He had taken a saline emetic some 15 minutes later and had vomited copiously since.

Course of Illness in the Hospital:-

On admission he was conscious with tremor of both arms and a warm, dry skin. Pulse 120 per minute and regular, blood pressure was not recorded. The chest was generally clear and the abdomen normal. Tendon reflexes were present. The pupils were dilated with some reaction to light.

Stomach washout was commenced soon after admission to the ward and recognisable tablets were obtained in the return. About five minutes after the washout he became completely disorientated and apparently hallucinated. This was followed directly by a grand mal fit which lasted for several minutes and which caused deep cyanosis. He was treated with oxygen and given paraldehyd intramuscularly. There followed about twenty minutes almost continuous fits after which he went into respiratory arrest and became completely flaccid. When the endotracheal tube was/

was eventually in position it was found that cardiac arrest was also present and cardiac massage and large amounts of bicarbonate were required to restore a relatively normal rhythm. The estimated duration of the cardiac arrest was about five to seven minutes. Clinically he was deeply unconscious and totally unresponsive to all stimuli. His pupils were widely dilated with no reaction to light.

His EEG record (Fig. 75) four hours after drug ingestion was isoelectric and showed no change even after painful stimulation of the sternum with the knuckles (Grade VII). His rectal temperature was 37.0°C and blood pressure 80/40 mm.Hg. He was on a Bird's respirator. After six hours of coma his record was still isoelectric and a record on higher gains (Fig. 76) showed no sign of cerebral electrical activity.

After 10 hours of coma his EEG record (Fig. 77) showed complete electrical silence (Grade VII). Clinically he was deeply unconscious and totally unresponsive to stimuli including stimulation of the sternum with the knuckles. His pulse was 124 per minute but the blood pressure was unrecordable despite metaraminol (Aramine) followed by over two litres of plasma under central venous monitoring control. The rectal temperature was 35.0°C . His EEG record showed no response to stimulation (Grade VII) and to exclude any technical fault in recording, the lead from the head box was pressed with the foot (Fig. 78) which produced an artefact, confirming the presence of an isoelectric record.

Sixteen/

EEG IN ORPHENADRINE AND PROMAXINE POISONING.

Patient 104 - Male, 41 years old.

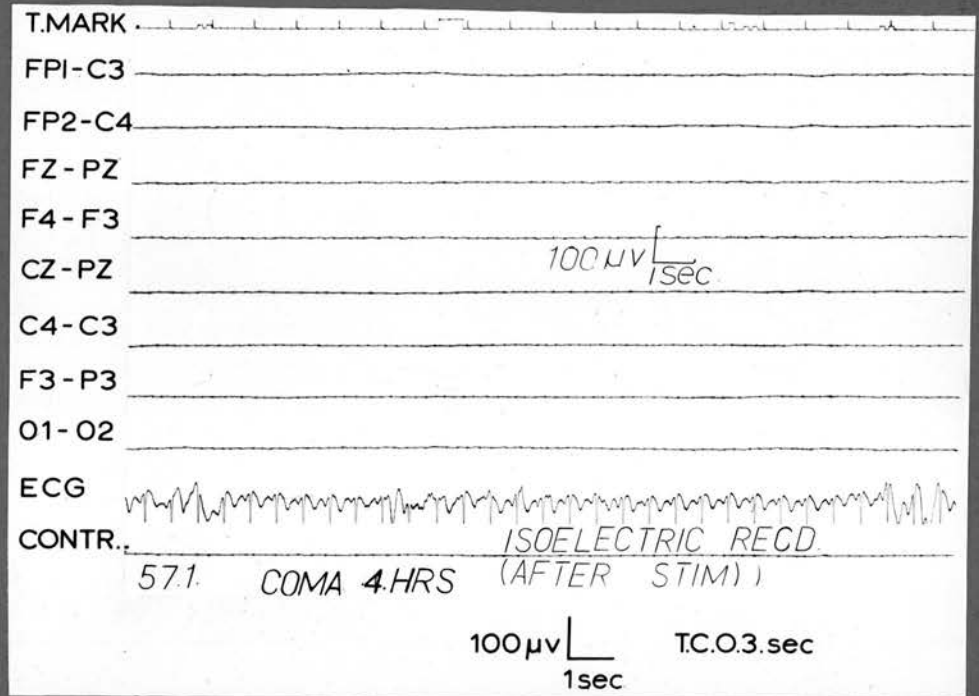


Figure 75:

His EEG record four hours after drug ingestion was isoelectric (Gains 100 μ V/cm). Rectal temperature 37.0°C. Clinically he was deeply unconscious and totally unresponsive to all stimuli.

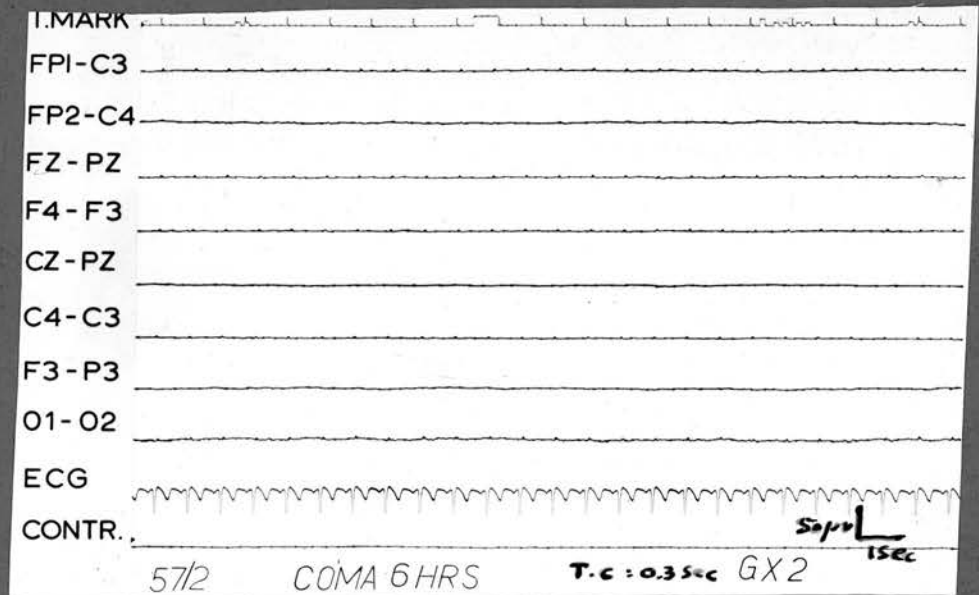


Figure 76:

After six hours of coma record was still isoelectric and a record on higher gains (50 μ V./cm; TC = 0.3 sec.) showed no sign of cerebral electrical activity (Grade VII).

EEG IN ORPHENADRINE AND PROMAZINE POISONING

Patient 104 - Male, 41 years old.

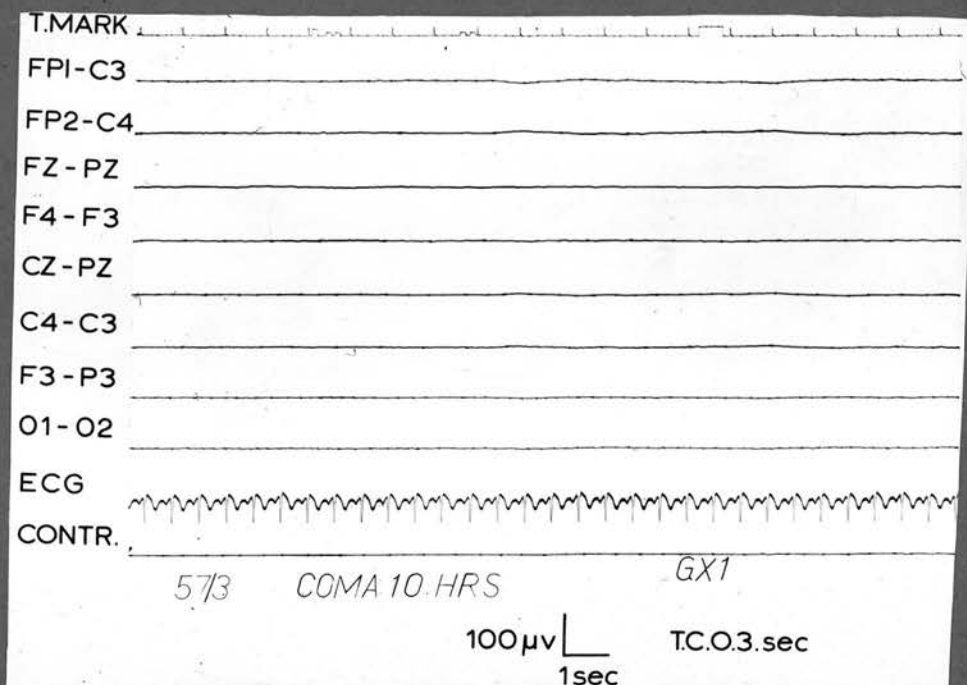


Figure 77:

After ten hours of coma this excerpt showed complete electrical silence (Grade VII). Rectal temperature 35.0°C; blood pressure unrecordable and pulse 124 per minute.

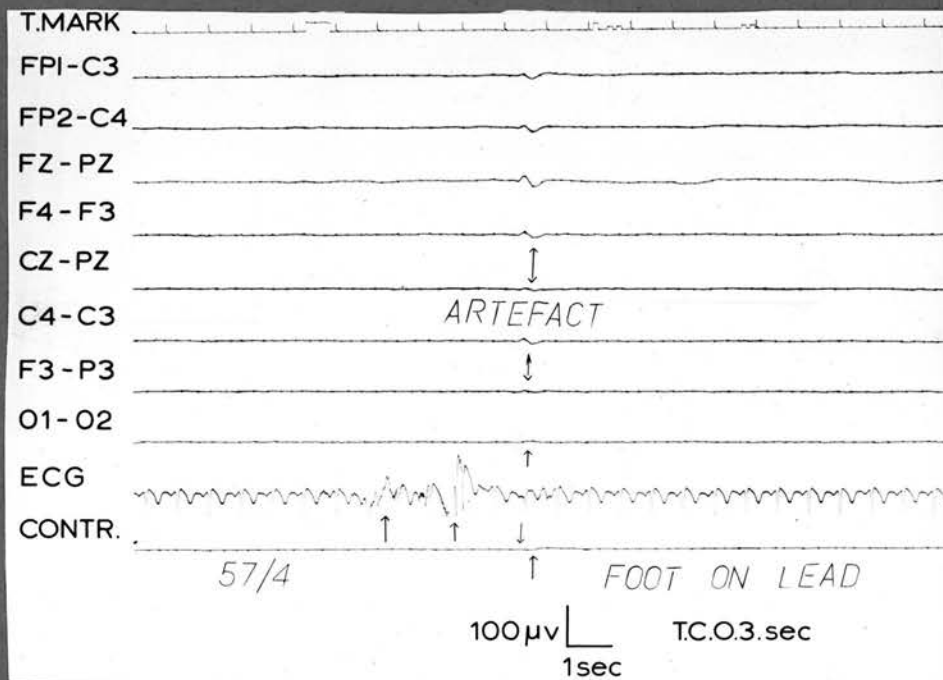


Figure 78:

Pressure on the lead from head box produced an artefact, confirming the presence of an isoelectric record.

Sixteen hours after drug ingestion EEG tracings were completely isoelectric (Grade VII) and a record (Fig. 79) taken at highest (maximum) gains ($20 \mu\text{v}/\text{cm.}$) contained ECG artefact at increased sensitivity but no signs of cerebral electrical activity. Clinically his condition remained unchanged, his pulse was 60 per minute and he required isoprenaline on several occasions for marked bradycardia. His blood pressure was unrecordable and rectal temperature 33.8°C . After twenty one hours of coma his EEG record (Fig. 80) was isoelectric and showed no change on sternal stimulation.

After twenty two hours of coma his EEG tracings (Fig. 81) were still completely isoelectric (Grade VII). The few isolated spike like deflections are artefacts. His heart rate was 12 per minute. Clinically he was deeply unconscious and totally unresponsive to all stimuli. His EEG record also remained unaffected by these stimuli. His blood pressure was unobtainable and rectal temperature was 32.4°C . Pupils were fixed and dilated. He died after 22 hours of coma. His EEG record (Fig. 82) remained isoelectric all this time (Grade VII).

A post mortem was performed which confirmed the diagnosis of cardiac arrest following poisoning with orphenadrine hydrochloride and promazine hydrochloride.

CASE HISTORY No. 7 (118/9/M.W.)

A female of 20 was admitted to the Edinburgh Poisoning Treatment Centre at 15.45 hours on the 4th February, 1968/

EEG IN ORPHENADRINE AND PROMAZINE POISONING

Patient 114 - Male - 41 years old.

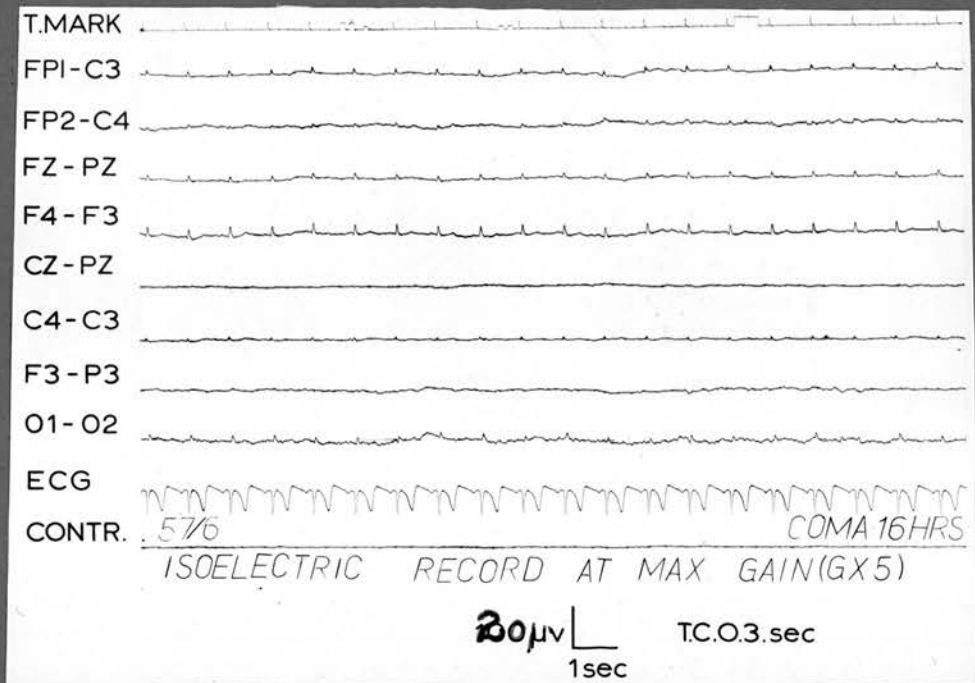


Figure 79:

Sixteen hours after drug ingestion EEG tracings were completely isoelectric and a record taken at maximum amplification (20 µv./cm) contained EEG artefacts at increased sensitivity but EEG remains isoelectric. Rectal temperature was 33.8°C, pulse 60 per minute and blood pressure unrecordable.

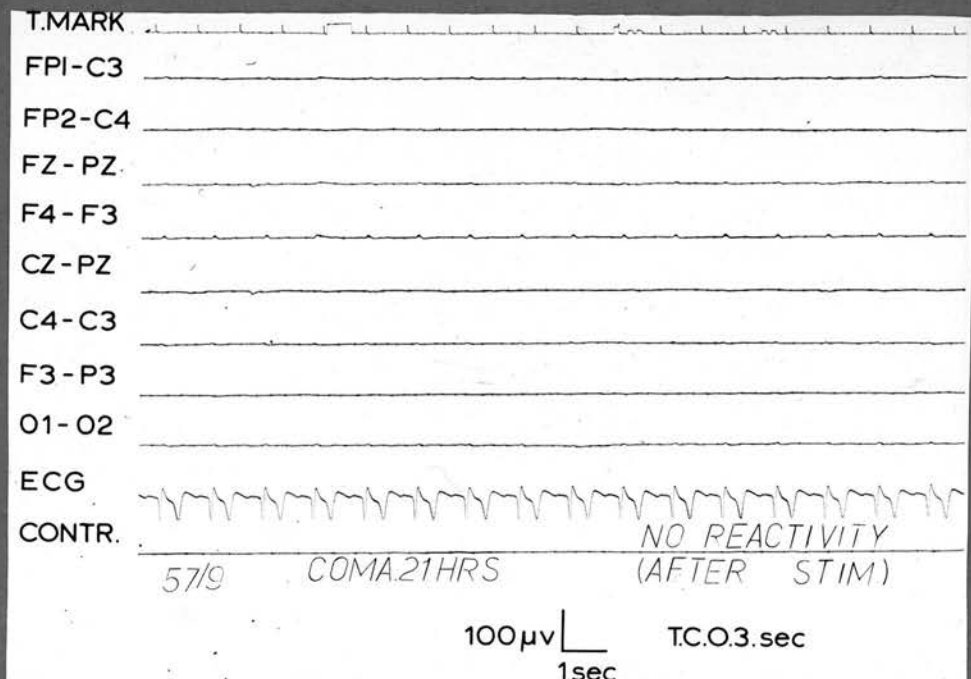


Figure 80:

After twenty one hours of coma his EEG record was isoelectric and showed no change on sternal stimulation.

EEG IN ORPHENADRINE AND PROMAZINE POISONING.
Patient 114 - Male 41 years old.

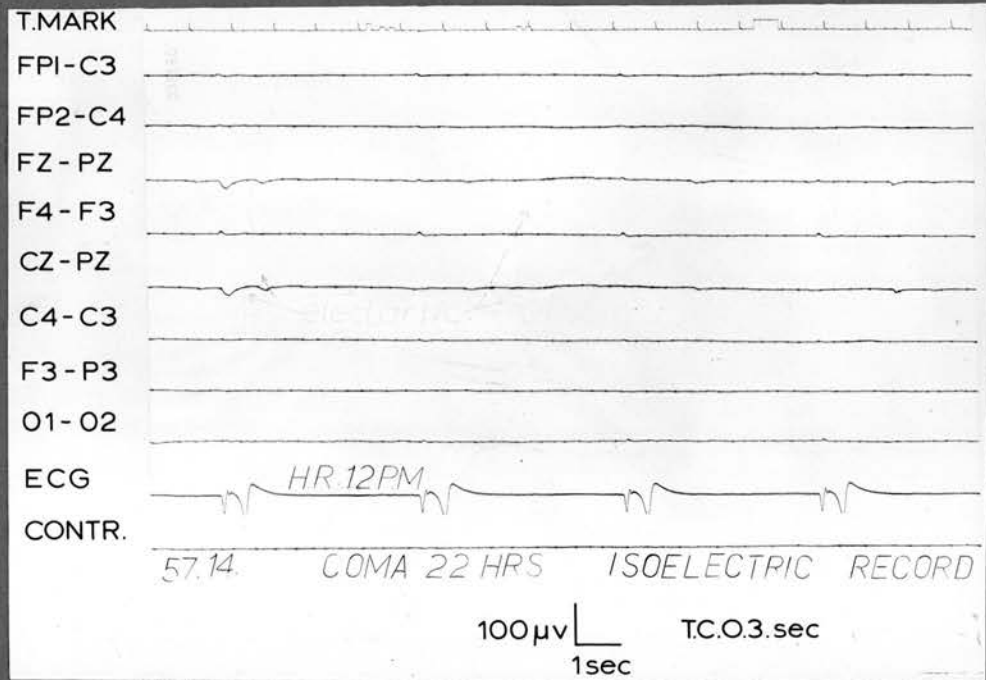


Figure 81:

Twenty two hours after ingestion of drugs his EEG tracings were still isoelectric (Grade VII). The few isolated spike like deflections are artefacts. His heart rate was 12 per minute and rectal temperature 32.4°C .

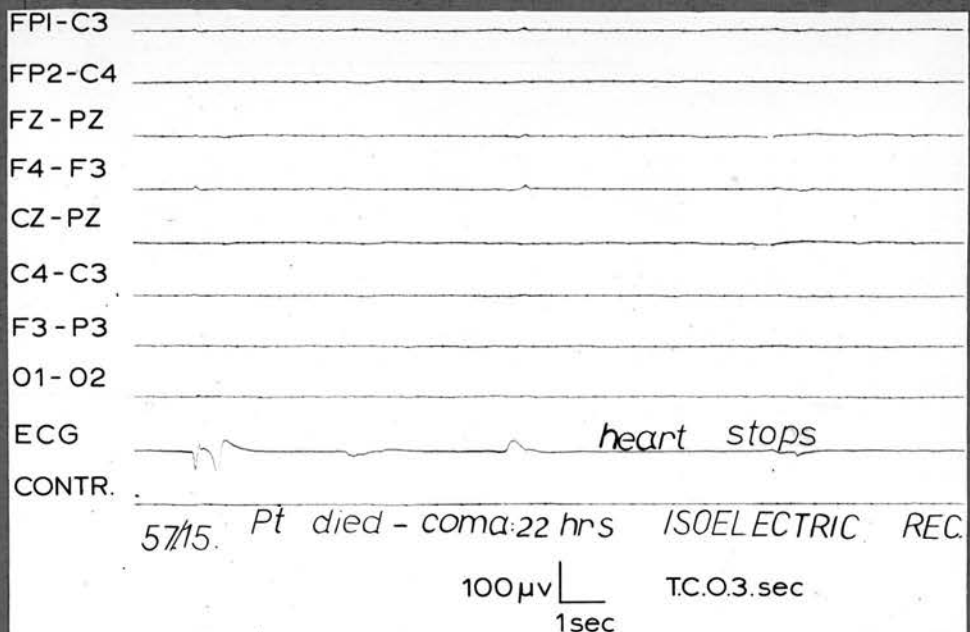


Figure 82:

After twenty two hours of coma his EEG record was still isoelectric when his heart stopped.

after having taken 20-24 tablets of meprobamate (400 mg. each) about 16-18 hours prior to admission.

Course of Illness in the Hospital:-

On admission she was deeply unconscious making minimal response to painful stimulation. Her pulse was 100 per minute, regular and of good volume; blood pressure 100/50 mm.Hg. and rectal temperature 36.6°C . Reflexes were present and slightly increased; the pupils were constricted and responded sluggishly to light. Physical examination, otherwise, was normal.

Her EEG twenty hours after drug ingestion (Fig. 83) showed continuous slow wave activity at $\frac{1}{2}$ -2 cps, superimposed on which was 12-14 cps fast activity. On sternal stimulation (Fig. 84) the activity was increased both in frequency and amplitude. The record contained background activity at 2-4 cps with superimposed 12-14 cps fast activity. The response to stimulation may also be seen in figure 85. The EEG consisted of 2-4 cps activity with superimposed 12-14 cps drug-induced fast activity.

After twenty two hours of coma her EEG record (Fig. 86) revealed spontaneous shifts, where 3-6 cps faster frequencies with superimposed 14-18 cps would alternate with $1\frac{1}{2}$ -3 cps slow wave activity. After 24 hours of coma the EEG record (Fig.87) contained 4-6 cps with burst of slow wave activity at 1-3 cps. Superimposed on these frequencies was 18-20 cps drug-induced fast activity.

Twenty/

EEG AFTER ACUTE MEPROBAMATE POISONING
Patient 118 - Female 20 Years Old.

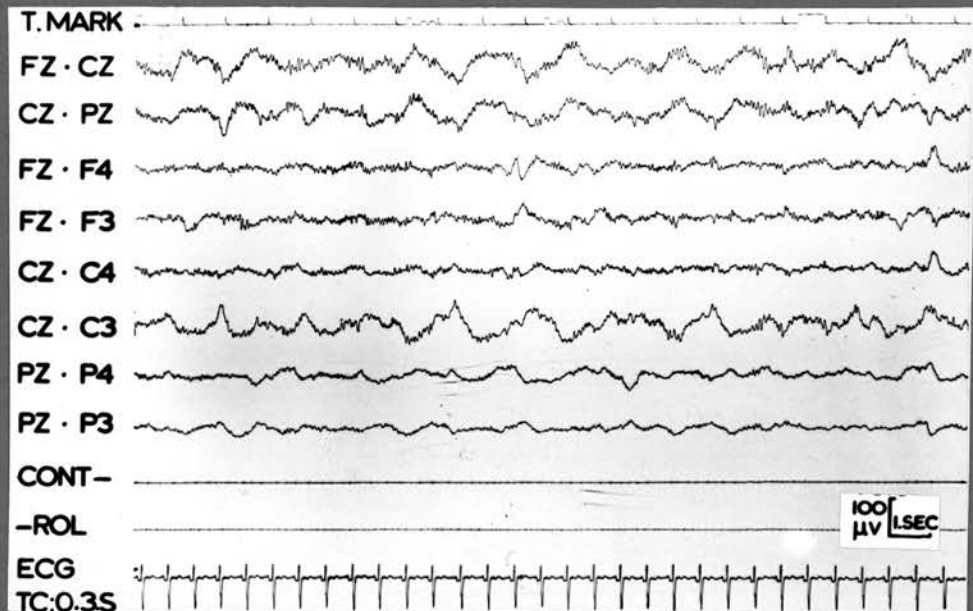


Figure 83:

Twenty hours after ingestion of meprobamate EEG tracings contained continuous $\frac{1}{2}$ -2 cps slow wave activity with superimposed 12-14 cps fast activity.

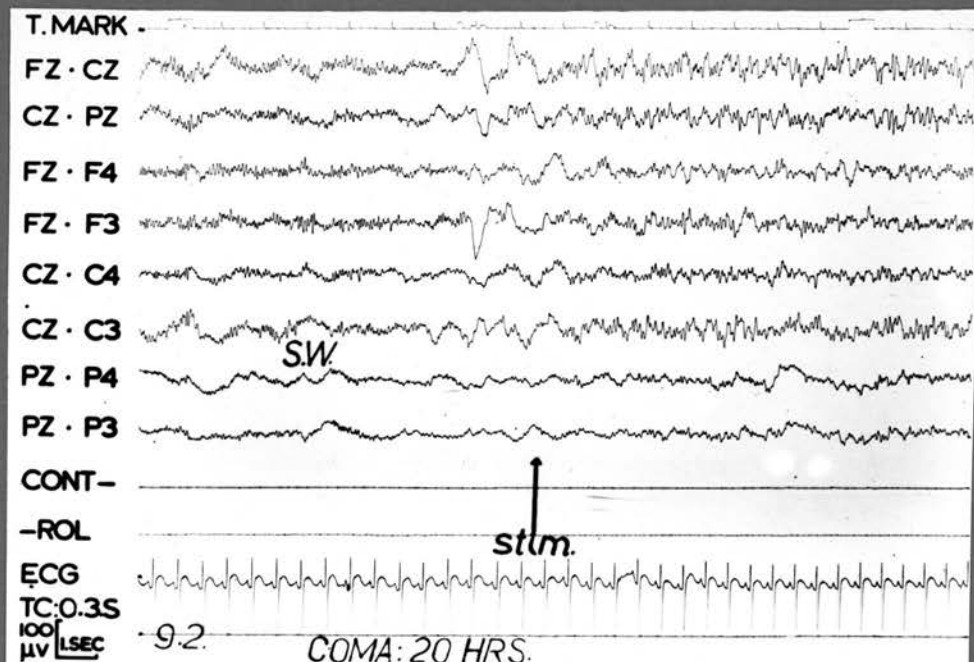


Figure 84:

This excerpt illustrates a response to sternal stimulation. EEG tracings showed $\frac{1}{2}$ -2 cps slow wave (SW) activity with superimposed fast activity. After stimulation the record consisted of background activity at 2-4 cps with superimposed 12-14 cps fast activity.

EEG AFTER ACUTE MEPROBAMATE POISONING
Patient 118 - Female - 20 years old.

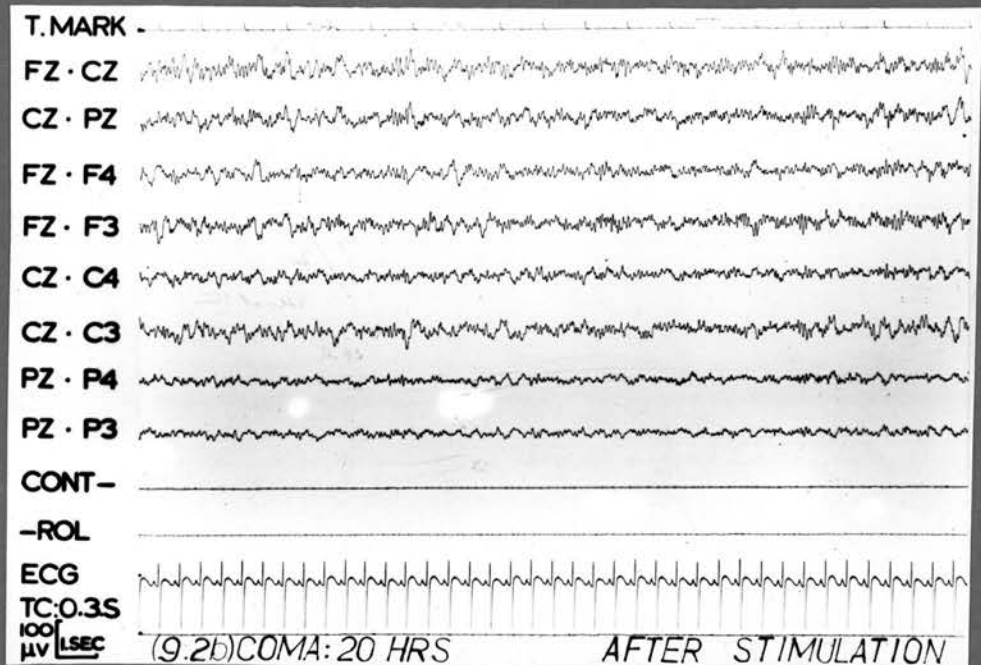


Figure 85:

After twenty hours of coma an EEG record after sternal stimulation showed dominant activity of 2-4 cps superimposed on which was 12-14 cps drug-induced fast activity.

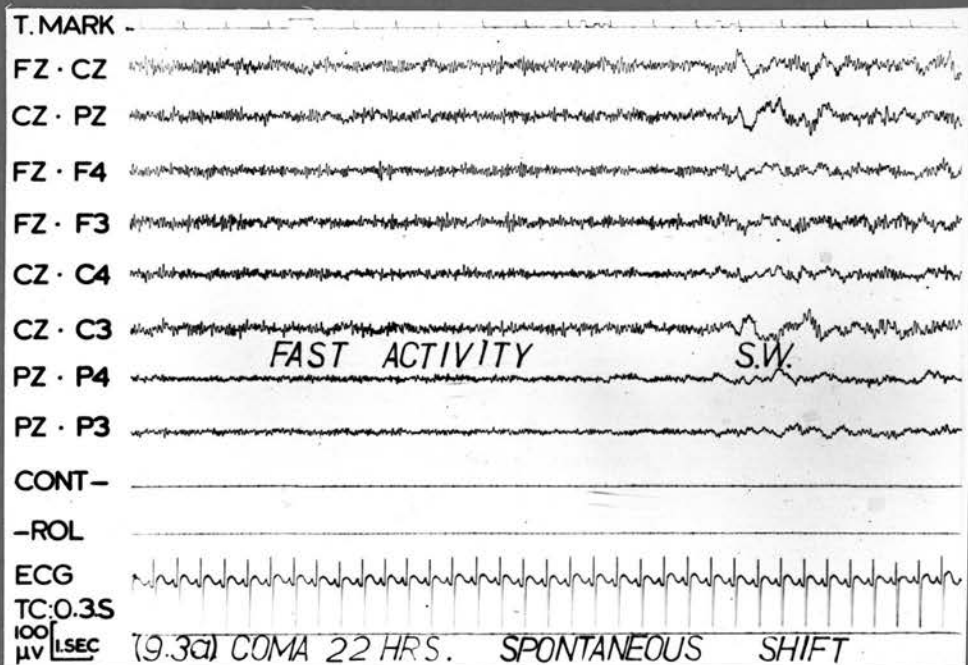


Figure 86:

Twenty two hours after lapsing into coma EEG record revealed spontaneous shifts in which 3-6 cps activity would give way to 1½-3 cps slow wave (SW) activity. An example is illustrated here.

EEG AFTER ACUTE MEPROBAMATE POISONING
Patient 118 - Female 20 years old.

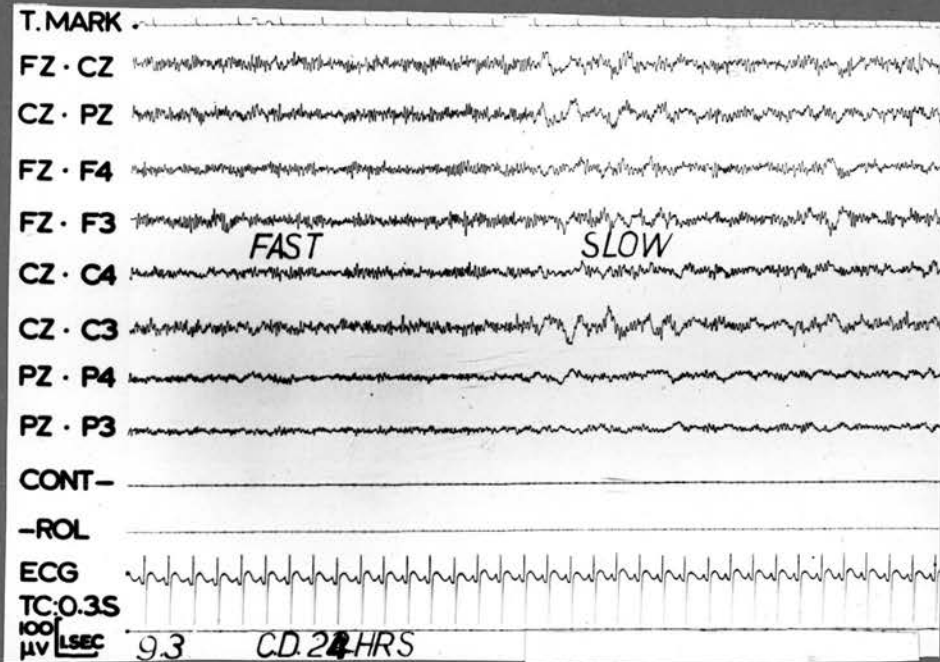


Figure 87:

After 24 hours of coma this excerpt shows fast background frequencies of 4-6 cps and a burst of slow wave activity at 1-3 cps. Superimposed on all these frequencies is 18-20 cps drug-induced fast activity.

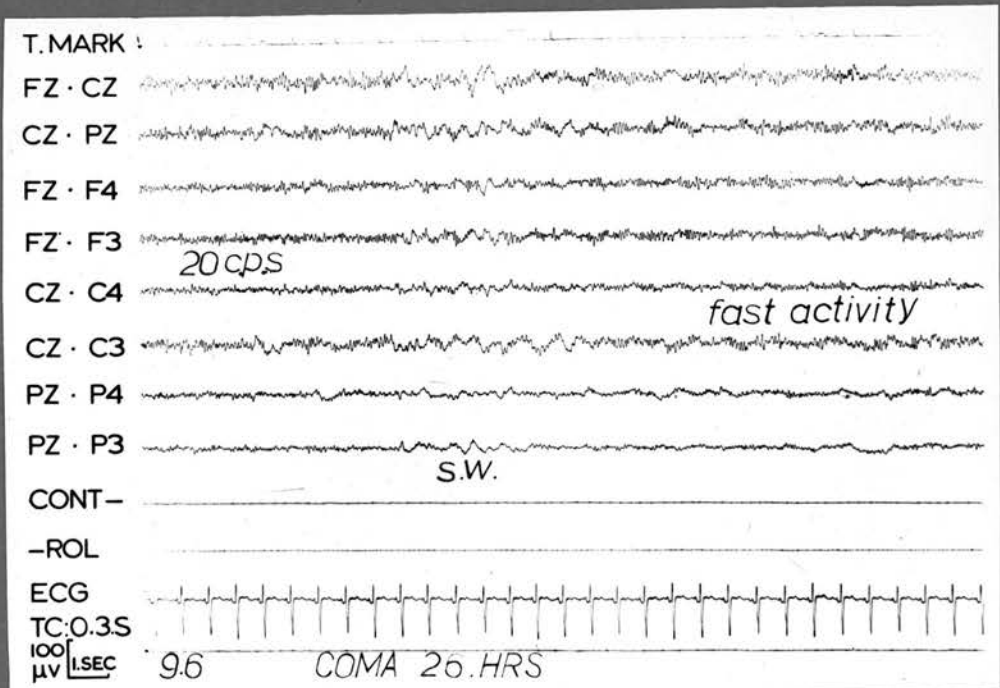


Figure 88:

Twenty six hours after lapsing into coma her EEG tracings contained background activity at 2-6 cps with superimposed 18-20 cps drug induced fast activity. Bursts of slow wave activity at $\frac{1}{2}$ -2 cps of 3-4 seconds duration were also present.

Twenty six hours after lapsing into coma she made vigorous response to painful stimulation of the sternum and her EEG record (Fig. 88) showed dominant activity at 2-6 cps with superimposed 18-20 cps drug-induced fast activity. Bursts of slow wave activity at $\frac{1}{2}$ -2 cps lasting for 3-4 seconds duration were also seen.

She continued to improve and responded to verbal command at the end of twenty eight hours. Her EEG record (Fig. 89) contained background activity of 4-6 cps with some 2-3 cps activity. Superimposed on these frequencies was drug-induced 18-20 cps fast activity.

Thirty six hours after drug ingestion (eight hours post-coma) the patient appeared asleep. Her EEG record (Fig. 90) showed a mixture of low voltage 4-6 cps and high voltage 2-3 cps activity. She responded to a vocal command by opening her eyes, when the high voltage slow waves also disappeared. The drug-induced fast activity (Fig. 91) was present even forty eight hours after ingestion of meprobamate.

Meprobamate concentration in blood was not estimated but her urine collected from 30.00 to 38.00 hours after drug ingestion was reported to contain a concentration of 80 mg. per 100 ml. The battery of psychological tests was administered 24 hours after regaining consciousness but no evidence of organic brain damage was detected.

EEG and psychometric tests were repeated at intervals of one, three and nine months but no abnormality was detected. Her EEG record (Fig. 92) one month after drug ingestion was normal.

EEG IN ACUTE MEPROBAMATE POISONING
Patient 118 - Female - 20 years Old.

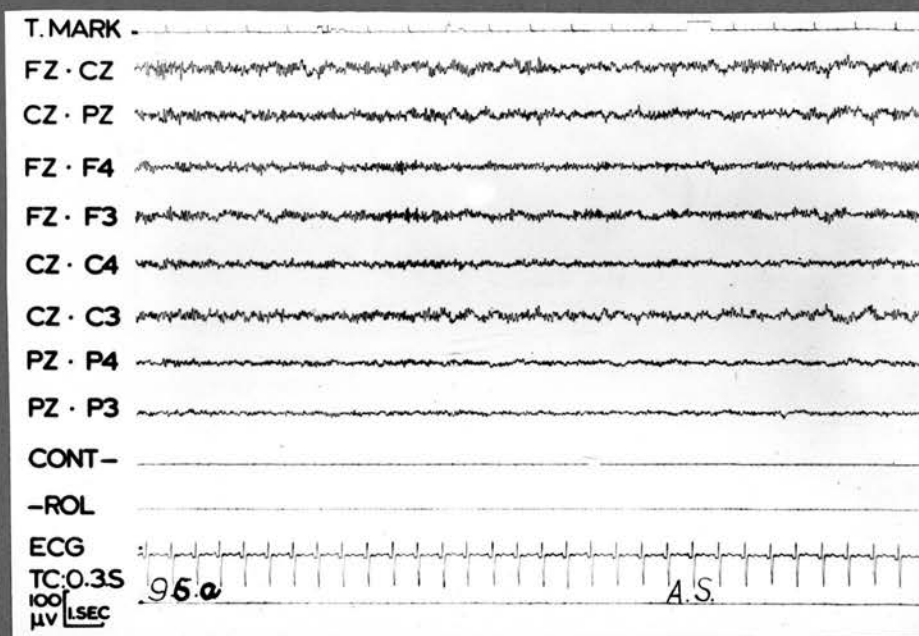


Figure 89:

After 28 hours of coma her EEG after sternal stimulation revealed dominant activity at 4-6 cps with some 2-3 cps activity. Superimposed on these frequencies was drug-induced 18-20 cps fast activity.

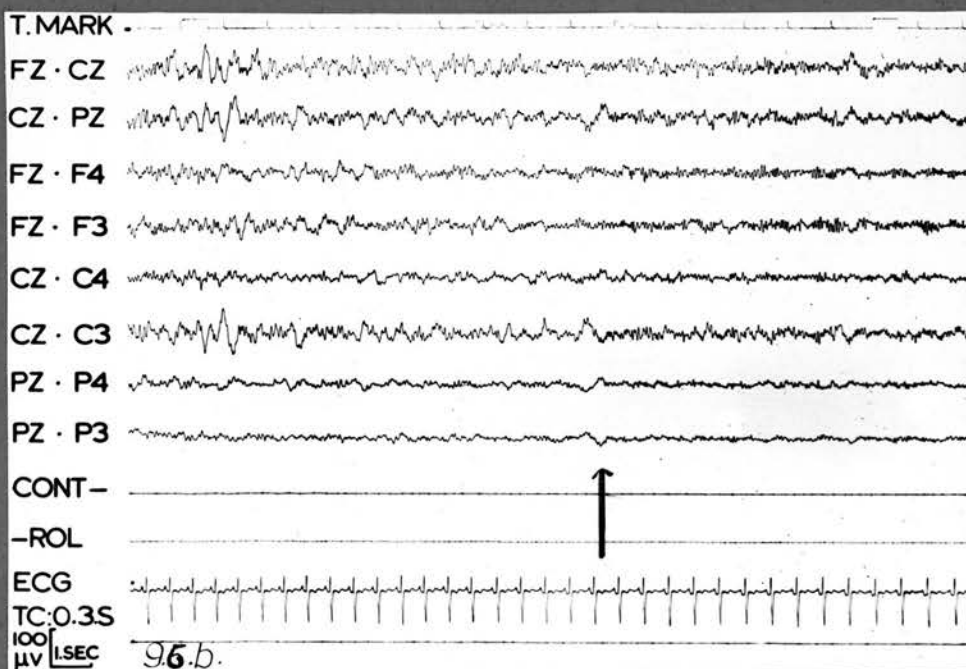


Figure 90:

Thirty six hours after drug ingestion (eight hours post coma) when the patient was asleep her record contained mixture of low voltage 4-6 cps and some high voltage 2-3 cps activity. She responded to a vocal command by opening her eyes (marked with the arrow) and the high voltage slow waves also disappeared.

Figure 91:

Forty eight hours after ingestion of meprobamate
(Twenty hours post coma) the EEG tracings still contained
drug-induced 18-20 cps fast activity.

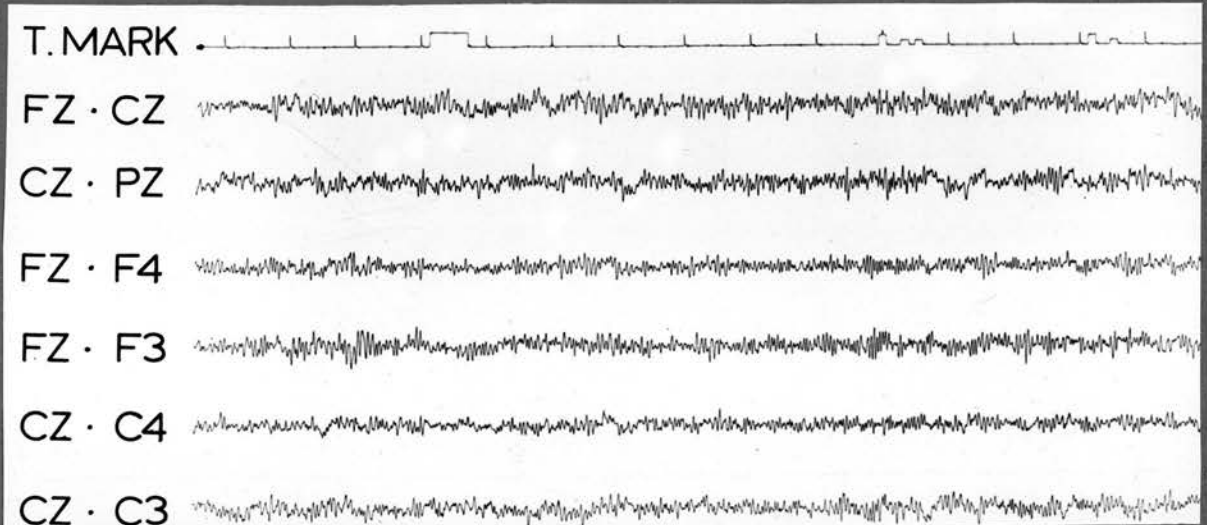
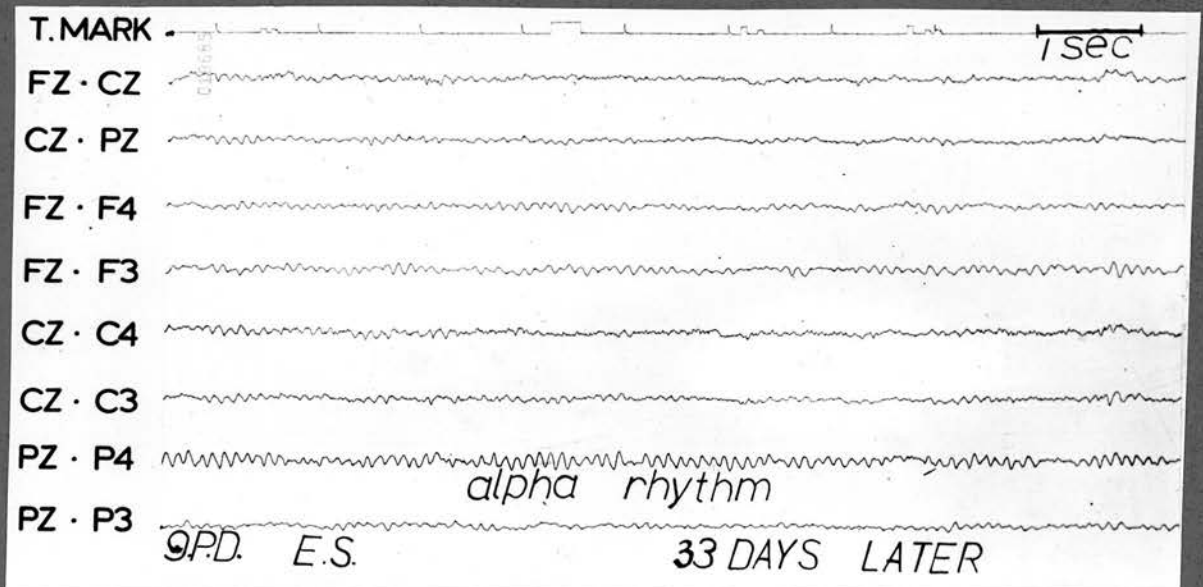


Figure 92:

Thirty three days after drug ingestion her EEG record showed
9-10 cps activity which was blocked by eyes opening.



CASE HISTORY No. 8 (82/99/E.J.)

A female of 19 was admitted to the Regional Poisoning Treatment Centre, Edinburgh at 09.00 hours on 26th February 1969, after having taken 40 tablets (200 mg.) of nitrazepam about nine hours prior to admission.

Course of Illness in the Hospital:-

On admission she was conscious and physical examination was normal. Her EEG record (Fig. 93) showed Grade I EEG abnormality as it revealed 18 cps activity. Her EEG 16 hours after drug ingestion (Fig. 94) showed 18 cps activity. On the same day she was seen by the Consultant Psychiatrist and transferred to the North Wing of the Royal Edinburgh Hospital for psychiatric in-patient care. Further studies with this patient are described in Project No. 3 (Patient No. 4.)

CASE HISTORY No.9 (117/101/N.R.)

A 36 year old female was admitted to the Regional Poisoning Treatment Centre, Edinburgh at 07.30 hours on the 1st March, 1969 after having taken 40 tablets (200 mg. each) of methyprylon (Noludar) approximately eight hours prior to admission.

Past History: She has two previous admissions to the hospital with similar overdoses. On her first admission in 1966, she had taken methyprylon (400 mg.) and became conscious four hours after admission. On first and second post-coma nights she was reported to be "restless" and "very poor night, only dozed off and on" and was/

EEG IN ACUTE NITRAZEPAM POISONING

Patient 82 - Female 19 years old.

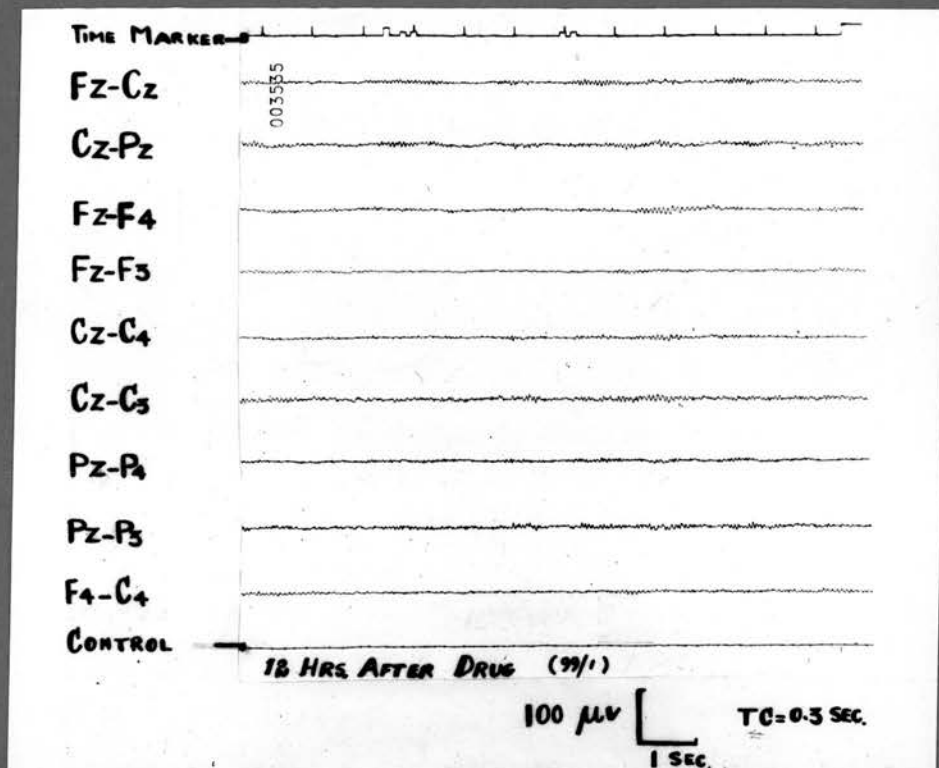


Figure 93:

Twelve hours after ingestion of 200 mg. nitrazepam EEG record revealed Grade I EEG abnormality. It contained 16-18 cps activity.

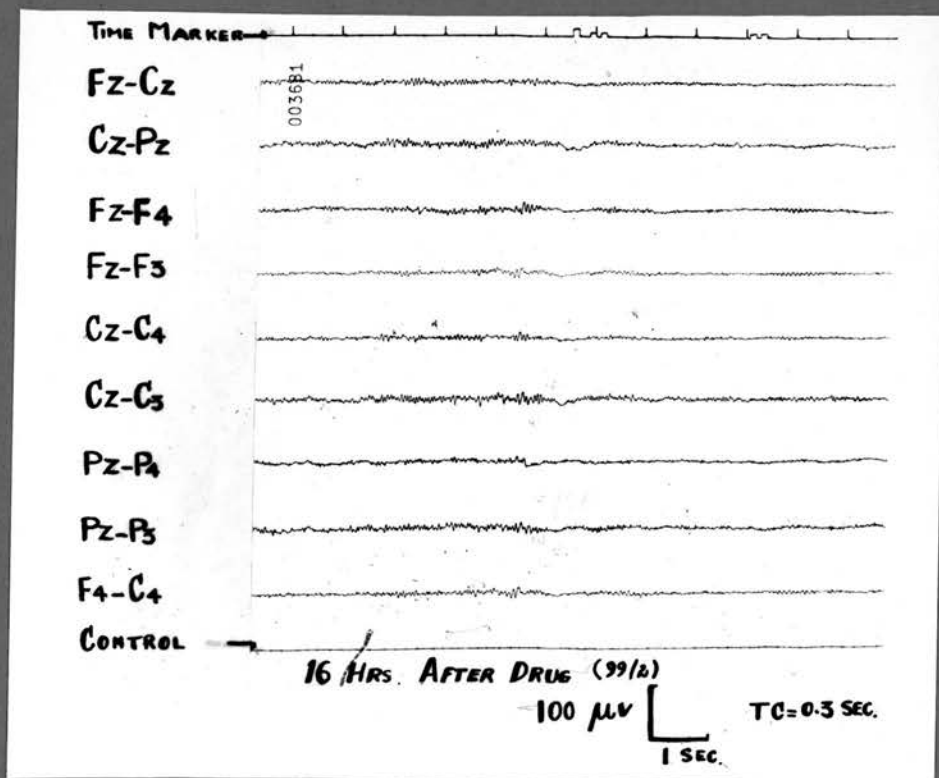


Figure 94:

This excerpt sixteen hours after drug ingestion shows 18 cps activity.

was prescribed sodium amylobarbitone 200 mg. as night sedation.

On her second admission in April, 1967 she had taken 20 tablets of Mandrax and her methaqualone level in blood on admission was 4.2 mg. percent. During recovery she was reported to be "terribly obstreperous" and required 50 mg. of chlorpromazine intramuscularly.

Course of the Present Illness:-

On admission she was deeply unconscious and made no response to stimulation of the sternum with the knuckles. Erythematous areas were noted over contact areas around knees, feet, thighs and the right ear. Pulse was 102 per minute, regular and good volume; blood pressure 80/60 mm. of Hg. Tendon reflexes were present but plantar responses were not elicited. Her pupils were dilated and reacted sluggishly to light but fundi were normal. Chest clinically clear but respiration was shallow and respiratory minute volume was 3.8 litres. Rectal temperature was 36.0°C.

No stomach washout was performed but intensive supportive therapy instituted. Her initial EEG record, ten hours after drug ingestion, showed Grade VI abnormality. It contained three isolated bursts of activity separated from each other by areas of electrical silence. Clinically she was in deep coma and unresponsive to stimulation. Her methyprylon level in the blood was 8.2 mg. percent and rectal temperature 35.8°C.

After twelve hours of coma her EEG record showed Grade V abnormality: 5-10 cps activity of several seconds duration would alternate with electrical silence. Clinically she was deeply unconscious/

unconscious and made no response to stimulation. Her blood methyprylon level was 5.6 mg. percent, rectal temperature 36.9°C and respiratory minute volume 5 litres.

Fifteen hours after drug ingestion her EEG record contained 1-4 cps activity with occasional brief isoelectric intervals (Grade IV) but clinically her condition remained unchanged. After 19 hours of coma her EEG showed continuous activity at 1-4 cps. Her drug levels was 3.5 mg. percent and rectal temperature 37.5°C . Clinically she made a minimum response to maximum stimulation.

After twenty four hours of coma her EEG showed Grade III abnormality. Her methyprylon level was reported to be 3.0 mg. percent and rectal temperature 36.4°C . Clinically she responded maximally to a minimal painful stimulation. She continued to improve and 28 hours after drug ingestion she responded appropriately to verbal commands.

Thirty six hours after drug ingestion her EEG showed Grade II abnormality. Her blood methyprylon concentration was 2.2 mg. percent and rectal temperature 36.5°C . Clinically she was drowsy. Four hours later she was seen by the consultant psychiatrist and transferred to the North Wing (Female Ward) of Royal Edinburgh Hospital for psychiatric in-patient care. A blood examination 96 hours after drug ingestion (68 hours post-coma) still showed presence of drug in a concentration of 1.6 mg. percent. A further account of this patient's recovery over the subsequent weeks is presented in project 3 (Patient No. 3.)

CASE HISTORY No. 10 (24/22/3F)

A 32 year old male was admitted to the Regional Poisoning Treatment Centre at 01.40 hours on the 18th March, 1968, after having taken about 100 sleeping tablets (quinalbarbitone) belonging to his wife, three hours prior to admission to the hospital. In 1965 he had been admitted to this centre after an overdose of a hypnotic.

Course of Illness in the Hospital:-

On admission he was deeply unconscious and made no response to any stimuli. His tendon reflexes were absent. His pulse was 92 per minute, regular; blood pressure 70/45 mm.Hg. and rectal temperature 35.5°C. No focal neurological signs were found. Respiration was depressed with a rate of 3-8 per minute with respiratory minute volume of 3 litres. Arterial blood gas analysis showed oxygen desaturation (47%) and barbiturate levels in the blood 1.9 mg.% as quinalbarbitone. An endotracheal tube was inserted and thereafter gastric aspiration and lavage carried out, successfully removing a proportion of the poison. Analysis of gastric aspirate was reported to contain quinalbarbitone and 165 mg. of the drug was recovered.

Continuous EEG monitoring was started soon after admission and his initial record showed complete electrical silence (Grade VII). After eight hours of coma his EEG tracings showed isolated bursts of activity (Grade VI) in response to stimulation of the sternum by rubbing with the knuckles. His rectal temperature was now 35.0°C and blood barbiturate level 1.7 mg.%.

Nine/

Nine hours after drug ingestion his blood oxygen saturation was 81%. Clinically he remained unchanged. After 12 hours of coma his EEG tracings contained spontaneous isolated bursts of 3-7 cps activity which would increase both in frequency and amplitude on stimulating the sternum of the patient.

After 14 hours of coma, the patient's EEG record deteriorated and the isolated bursts of activity seen before disappeared. His rectal temperature was 36.1°C , respiratory minute volume 7.4 litres, arterial blood oxygen saturation 81% and barbiturate level 2.2 mg.%. Clinically the patient's condition showed no change.

Eighteen hours after drug ingestion the spontaneous activity returned in his EEG record (Grade VI) and thereafter continued to improve. Twenty hours after lapsing into coma his EEG record showed suppression burst activity (Grade V). Clinically the patient was deeply unconscious and unresponsive to all stimuli. His temperature rose to 37.8°C . Three hours later he made the first clinical response to stimulation. EEG record consisted of continuous slow waves (Grade IV). His temperature was 38.8°C and blood barbiturate level 1.7 mg.%. After 34 hours of coma EEG tracings showed Grade IV changes. His blood barbiturate level was 1.3 mg.% and rectal temperature 38.3°C . Clinically he made minimal response to a maximal painful stimulation. Eight hours later his endotracheal tube was removed.

Forty five hours after drug ingestion he responded vigorously to painful stimulation; his EEG revealed Grade III abnormality. His temperature was 37.8°C and blood barbiturate level 0.8 mg.%. After sixty three hours of coma, the patient responded/

responded appropriately to vocal command. His barbiturate level was 0.4 mg.% and body temperature was 37.2°C. Forty eight hours after regaining consciousness a battery of psychological tests was administered, but no evidence of any organic brain damage was found. EEG and psychometric tests repeated after one, three and nine months were normal.

CASE HISTORY No. 11 (25/40/B.B.)

A 26 year old female took 60-70 capsules (100 mg. each) of seconal (Sodium quinalbarbitone) at about 03.00 hours on the 14th June, 1968, and was admitted to the Regional Poisoning Treatment Centre, Edinburgh Royal Infirmary at 16.40 hours on the same day.

Course of Illness in the Hospital:-

On admission she was deeply unconscious with no response to any stimuli. The pulse was 130 per minute regular, but poor in volume and blood pressure was 90/60 mm.Hg. Tendon reflexes were absent and muscle tone flaccid. Cough, corneal and gag reflexes were absent and so were the bowel sounds. No focal neurological signs were found. There was bronchial breathing at the right lung base with some crepitations. Examination otherwise was normal. An endotracheal tube was inserted but gastric lavage and aspiration were not carried out in view of the time that had elapsed since the tablets were taken. Arterial blood gas analysis showed oxygen desaturation and a chest X-ray showed consolidation in the right lung. Her rectal temperature was 39.4°C and blood barbiturate level 0.7 mg.% as quinalbarbitone.

Continuous EEG monitoring started two hours after her admission to the ward. The record showed complete electrical silence/

(Grade VII) and remained isoelectric even on ~~Maximum~~ gain location (20 $\mu\text{v}/\text{cm}$). Clinically she was deeply unconscious and totally unresponsive to all stimuli including rubbing of the sternum with the knuckles. After 22.50 hours of coma her EEG showed isolated bursts of activity (Grade VI). Her rectal temperature was 39.5°C and blood barbiturate concentration 1.0 mg.% as quinalbarbitone.

After 26 hours of coma EEG tracings showed suppression-burst activity (Grade V). Her blood barbiturate level was 1.0 mg.% and temperature 39.7°C . Clinically she was deeply unconscious and made no response to sternal stimulation. Her barbiturate level after 33 hours was 0.8 mg.% and temperature 38.3°C . Thirty six hours after drug ingestion a clinical response was observed to sternal stimulation.

After 52 hours of coma her EEG tracings showed Grade III abnormality. Her barbiturate concentration was 0.6 mg.%. Clinically she responded vigorously to painful stimulation. Thereafter she continued to improve slowly and after remaining in coma for 54 hours she regained consciousness. Her barbiturate level was still 0.7 mg.% which in fact was the same as on admission. Her EEG showed Grade II EEG abnormality. Sixty two hours after drug ingestion her blood barbiturate concentration was less than 0.5 mg.% and temperature 37.0°C .

On her 5th hospital night (two post-coma nights) she complained of insomnia, for which she was prescribed dichloralphenazone 1300 mg. as night sedation, which was discontinued on 13th July when nitrazepam 10 mg. was prescribed.

Eight days after drug ingestion (5 post-coma days) she was/

administered a battery of psychological tests but no evidence of any brain damage was found. EEG and psychological tests were repeated at intervals of one, three and nine months but no abnormality was found.

CASE HISTORY No. 12 (27/52/WR)

A 48 year old female took 90 of her own quinalbarbitone (Seconal) tablets at about 09.00 hours on the 18th October, 1968 and was found unconscious at 12.30 hours. She was apnoeic and cyanosed. The Family Doctor instituted external cardiac massage and artificial respiration and she was admitted to the Regional Poisoning Treatment Centre, Edinburgh.

Course of Illness in the Hospital:-

On admission to the hospital she was deeply unconscious and made no response to any stimuli. Her pulse was 80 per minute and regular, blood pressure 85/40 mm.Hg. Her breathing was depressed though present. An endotracheal tube was inserted and assisted respiration instituted. Tendon reflexes, cough, corneal and gag reflexes were all absent and so were the bowel sounds. Her pupils were fixed, dilated and did not react to light. Her rectal temperature was 33.8°C. During stomach washout she had a cardiac arrest but was resuscitated. Her ECG showed sinus bradycardia with a rate of 48 per minute. She remained hypotensive and was put on a respirator.

Her electroencephalogram soon after admission showed complete electrical silence (Grade VII). Clinically she was still deeply unconscious and totally unresponsive to all stimuli. The barbiturate concentration in the blood was 5.8 mg.% as quinalbarbitone/

barbitone. After 15 hours of coma, her EEG tracings were still isoelectric (Grade VII) and showed no change to stimulation of the sternum with the knuckles. Her rectal temperature was 34.1°C and she was on the respirator. After 28 hours of coma her EEG record was still isoelectric. Her temperature rose to 37.2°C but clinically she showed no improvement. Three hours later her EEG record showed two isolated bursts of activity on maximal stimulation. Her blood barbiturate level was 4.5 mg.%.

Thirty four hours after drug ingestion, the EEG tracings showed spontaneous isolated bursts of activity at 3-7 ops occurring every 15-20 seconds (Grade VI). After 36 hours of coma her record showed suppression-burst activity (Grade V). Clinically she was deeply unconscious and made no response to sternal stimulation. Her temperature was 37.8°C . After thirty eight hours of coma the patient's cough and swallowing reflexes returned but she made no clinical response to sternal stimulation, although an increase both in frequency and amplitude of electrical activity was seen. Four hours later her record showed continuous activity (Grade IV).

Forty nine hours after drug ingestion, the patient was able to resume spontaneous breathing and was taken off the ventilator. Her minute volume was 4.5 litres and temperature 38.3°C . Clinically she now responded minimally to a maximal painful stimulation. After 56 hours of coma the patient's EEG record showed Grade III abnormality. Her temperature was 38.0°C . Five hours later the patient was extubated. Her EEG record/

record continued to improve and after 64 hours it revealed Grade III changes. Her temperature was 38.5°C. Thereafter the patient continued to improve satisfactorily and finally responded appropriately to vocal commands after 71 hours of coma; her rectal temperature was 37.5°C.

Eighty three hours after drug ingestion, although the patient was fully conscious, she was drowsy, confused and expressed paranoid ideas. Over the next 20 hours, she became less drowsy but her delusions became paramount in her mind. She herself denied taking any tablets and was convinced that she was not in the Royal Infirmary and that someone else had done this thing to her.

Ninety eight hours after drug ingestion (27 hours post-coma) she was declared medically fit and was seen by the consultant psychiatrist who elicited delusions; as she said, "I have been watched. They know everything about me. This is not the R.I.E." The following day (5th hospital day) she was transferred to a psychiatric in-patient unit at the Royal Edinburgh Hospital.

CASE HISTORY No. 13 (39/34/L.O.)

A 54 year old female took large quantity of butobarbitone (Soneryl) at about 03.00 hours on 1st June, 1968. She was admitted to the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh at 09.00 hours on the same day. In the ambulance en route to the hospital she had apparently had a cardiac arrest and when she came to the ward she was gravely ill. She had been attending the psychiatric out-patient clinic for a depressive illness./

Course of Illness in the Hospital:-

On admission she was deeply unconscious and unresponsive to all stimuli. Her pulse was 92 per minute, regular and good volume. Blood pressure, despite her deep coma, was markedly raised at 220/140 mm.Hg. Tendon reflexes were absent and muscle tone flaccid. Cough, corneal and gag reflexes were absent, as were bowel sounds. Light reflexes were also absent. An endotracheal tube was inserted and thereafter she required assisted ventilation with a ventilator, as blood gas analysis had shown marked hypoxia. Her rectal temperature was 32.2°C and blood butobarbitone concentration 7.1 mg.% as barbitone.

Continuous EEG monitoring was started soon after admission and this revealed a complete electrical silence (Grade VII). Twelve hours after drug ingestion, her rectal temperature was 31.0°C and blood barbiturate level 7.0mg.%. Fourteen hours after drug ingestion, forced alkaline diuresis was commenced. One hour later her EEG record was still isoelectric even on maximum amplification ($20\text{ }\mu\text{v/cm}$). Her rectal temperature was 30.6°C . After 18 hours EEG tracings showed an isolated burst of activity (Grade VI) on sternal stimulation.

After 24 hours of coma her EEG revealed spontaneous isolated bursts of activity (Grade VI). Her temperature was 33.6°C and blood butobarbitone level 6.6 mg.%. Clinically she was deeply unconscious and made no response to any stimuli but resumed spontaneous breathing and was taken off respirator.

Thirty eight hours after drug ingestion her EEG record showed Grade V changes. EEG activity would increase both in frequency and amplitude when the patient was stimulated by rubbing/

rubbing the sternum with the knuckles. Her rectal temperature was 36.4°C and butobarbitone level 6.2 mg.%. After 45 hours of coma her butobarbitone level was 5.9 mg.% and temperature 37.8°C . Her ECG recorded at this time revealed a sinus tachycardia and right bundle branch block.

After 52 hours of coma her EEG showed Grade IV abnormality. Four hours later the patient was extubated. Sixty hours after drug ingestion she made a clinical response to painful stimulation. Her rectal temperature was 38.2°C and blood butobarbitone level 4.0 mg.%. Eighteen hours later the butobarbitone level dropped to 2.5 mg.% and clinically she responded moderately to painful stimuli. Arterial blood oxygen saturation was 60%. The EEG record continued to show improvement but was still Grade IV. Eighty hours after drug ingestion the EEG record showed Grade III abnormalities and three hours later the patient's response to painful stimulation became vigorous. Her temperature was 37.8°C and blood butobarbitone level 1.8 mg.%.

After 89 hours of coma she responded appropriately to a verbal command, but remained drowsy and confused. Her temperature was 37.0°C and butobarbitone 1.5 mg.%. On the 5th post-coma day she was still very confused and paranoid and on the 19th hospital day (15 days post-coma) she was transferred to the Royal Edinburgh Hospital for psychiatric in-patient care.

CASE HISTORY No. 14 (8/93/MG)

A 23 year old female was admitted to the Regional Poisoning Treatment Centre at 16.30 hours on the 3rd February 1968/

1968, after having taken an unknown quantity of amitriptyline tablets approximately twelve hours prior to admission.

Course of Illness in the Hospital:-

On admission she was deeply unconscious, responding minimally to stimulation of the sternum with the knuckles. Her pulse was 120 per minute, regular and of good volume and the blood pressure was 120/90 mm.Hg. Tendon reflexes were present and increased and plantar reflexes extensor. Muscle tone was increased and the patient exhibited intermittent episodes of general bilateral twitching with hypertonicity. Cough and gag reflexes were present but the corneal reflex was absent. The pupils were dilated, equal and reacted poorly to light. Bowel sounds were present but rare. Gastric lavage was done and intensive supportive therapy instituted.

Her EEG record after admission showed Grade IV abnormality and contained continuous 1-3 cps activity which would increase both in frequency and amplitude following sternal stimulation. Her rectal temperature was 35.8°C. After 15 hours of coma her EEG was of Grade III abnormality, and clinically she made moderate responses to painful stimulation. Her rectal temperature was 36.4°C. Seventeen hours after drug ingestion her ECG record showed non-specific changes, with sinus tachycardia of 120 per minute, and a PR interval of 0.14 seconds.

Nineteen hours after drug ingestion her EEG record showed Grade II abnormality, it contained dominant activity at 5-8 cps mixed with which was some 6-12 cps activity. Clinically the/
the/

patient made appropriate response to verbal commands. Her rectal temperature was 37.2°C and examination of the urine showed it to contain a fair amount of amitriptyline.

After 28 hours (nine hours post-coma) she had hallucinations which disappeared on the 3rd day and she was discharged home on the 4th hospital day.

CASE HISTORY No. 15 (108/59/O.G.)

A 31 year old male was admitted to the Regional Poisoning Treatment Centre on 13th December, 1968, at 13.45 hours, after having been found by the police staggering about the street, acting strangely. Initially he was taken to the People's Palace where he had a major fit and was then brought to the hospital.

Past History:- He had been partially investigated for fits in April 1967, but had not kept an EEG outpatient appointment. He had been maintained on 30 mg. phenobarbitone daily.

Course of Illness in the Hospital:-

On admission he was deeply unconscious and unresponsive to any stimuli. He was cyanosed and required intubation and was put on a respirator. His pulse was 100 per minute, regular and blood pressure 130/90 mm.Hg. Muscle tone was markedly reduced in all limbs with residual knee jerks and no obtainable plantar responses. Chest examination revealed many coarse crepitations in both lung fields. No bowel sounds were heard and soon after admission his pupils became dilated and fixed. His rectal temperature was 32.2°C . Gastric aspiration and lavage were performed and tablets and alcohol were observed to be in the return.

Continuous EEG monitoring was commenced two hours after admission and his EEG record was isoelectric. It did not show any/

any change to stimuli (Grade VII) including stimulation of the sternum with the knuckles. Clinically he was in deep coma and made no response to any stimuli. His systolic blood pressure was 90 mm.Hg. and temperature 31.9°C .

Eight hours after admission his EEG tracings showed complete electrical silence which remained unchanged on maximum gains ($20\ \mu\text{v}/\text{cm}$) as well as after stimulation of the sternum with the knuckles (Grade VII). Clinically his condition deteriorated. His pulse fell to 48 per minute. His temperature and blood pressure followed a gradual downward trend despite an initial injection of metaraminol followed by intravenous plasma under central venous monitoring and heavy wrapping in blankets. These measures appeared to have no effect. Examination of his blood for the detection and estimation of drugs revealed barbiturates at 1.1 mg. percent.

After 12 hours of coma his EEG record showed complete electrical silence and no change was seen on maximum gains (Grade VII). Clinically his condition remained unchanged. His rectal temperature was 30.4°C and blood pressure 70 mm.Hg. systolic. He was noted to have bilateral papilloedema but no localising CNS signs. The neurosurgeons were called to see him but considered that there was nothing they could offer.

After 24 hours his EEG tracings showed no sign of cerebral electrical activity and no change was seen after stimulation (Grade VII). A record taken at maximum gains ($20\ \mu\text{v}/\text{cm}$) showed an isoelectric record. Clinically he was deeply unconscious and totally unresponsive to all stimuli. His pupils were dilated and/

and fixed and did not react to light. His pulse was 32 per minute, blood pressure 55 mm.Hg. systolic and rectal temperature 29.8°C. He was on respirator. No significant poison was discovered in blood or urine (only therapeutic levels of barbiturate).

His condition continued to deteriorate and he died on the 14th December, 1968. A provisional diagnosis of intracerebral haemorrhage was made. A post mortem was performed and histological examination of the brain sections showed probable astrocytoma of frontal lobe.

CASE HISTORY No. 16 (110/60/JL)

A 40 year old female was admitted to the Regional Poisoning Treatment Centre, Edinburgh on the 26th December, 1968 at 19.30 hours after having taken 20 tablets of Diconal^{*} and 10 tablets of Mandrax.

Course of Present Illness in the Hospital:-

On admission she was deeply unconscious and totally unresponsive to all stimuli. Her pulse was 60 per minute, regular and of poor volume; blood pressure 60 mm.Hg. systolic; respiration was shallow and inadequate and she was cyanosed. All tendon reflexes were absent and plantar reflexes could not be elicited. Muscle tone was markedly reduced. Cough, corneal and gag reflexes were absent but bowel sounds were audible. The pupils were fixed, dilated and equal. Her rectal temperature was 35.0°C. She was intubated and hand ventilation served to correct the anoxia, and the pupils became pinpoint in size.

Gastric aspiration and lavage were performed with a small quantity of pink material in the return. Her respiratory minute volume was 2.5 litres. She was given nalorphine 20 mg. intravenously after which spontaneous respiration returned in 5-7 minutes and her respiratory minute volume was 4.5 litres but no change was seen in the level of coma. Thirty minutes later nalorphine 5 mg. intravenously was repeated.

^{*} Diconal is a combination of dipipanone 10 mg. and cyclizine.

Continuous EEG monitoring was commenced two hours after admission and her record showed Grade VI abnormality. It contained near silence but with two bursts of isolated and low voltage 3-7 cps waves occurring singly in each epoch. Clinically she was in deep coma and totally unresponsive to all stimuli. Her blood pressure was 80/60 mm.Hg. and rectal temperature 35.2°C. Blood examination for drug levels was reported to contain methaqualone 1.5 mg. percent. Eight hours after drug ingestion her EEG record showed suppression burst activity (Grade V). Her respiration rate was 16 per minute, respiratory minute volume 3.5 litres; temperature 35.5°C and blood pressure 85 mm.Hg. systolic. Nalorphine 5 mg. was repeated. Two hours later her EEG record showed Grade IV abnormality.

After 12 hours of coma her EEG record deteriorated and showed Grade V abnormality. Clinically the patient was deeply unconscious and made no response to painful stimulation of the sternum. Her respiration rate was 10 per minute, temperature 35.5°C and blood pressure 100/60 mm.Hg. One hour later her respiration rate was 7 per minute. Fourteen hours after drug ingestion her EEG record contained suppression burst activity. Her respiration rate was 10 per minute, respiratory minute volume of 3.5 litres, blood pressure 100/60 mm.Hg. and rectal temperature 36.6°C.

After 16 hours of coma the patient was given nalorphine and her respiration rate rose from 9 per minute to 18 per minute and her respiratory minute volume became 5.5 litres. Her rectal temperature was 37.8°C. A rapid infusion of nalorphine 30 mg. in 500 ml. of saline over 30 minutes improved her respiratory minute/

minute volume to 8 litres, with a respiration rate of 24 per minute. Clinically her pupils were larger and she responded moderately to painful stimulation. Her EEG record revealed Grade IV abnormality. Nalorphine 30 mg. was repeated after 17 hours of coma. Her blood pressure was 100/60 mm.Hg., rectal temperature was 37.8°C , respiration 20 per minute and respiratory minute volume 6 litres.

Eighteen hours after drug ingestion her EEG record contained dominant activity at 1-2 cps (Grade IV). Clinically she made vigorous response to painful stimulation. Examination of the urine revealed methaqualone (10 mg. percent), diphenhydramine and dipipanone hydrochloride together with some proteins and sugar. After 24 hours of coma the EEG record showed Grade III abnormality. Clinically the patient was unconscious but responded vigorously to painful stimulation. Her respiration rate was 22 per minute; respiratory minute volume 6 litres and rectal temperature 38.3°C . She continued to improve and 41 hours after drug ingestion she was extubated. Her blood pressure was 130/80 mm.Hg., respiration 10 per minute and temperature 38.3°C .

Forty five hours after lapsing into coma her EEG record contained dominant activity at 2-4 cps. mixed with which was some 3-6 cps activity. Clinically she made appropriate responses to vocal commands but remained very drowsy and confused for the next 48 hours.

On her 5th hospital night (2 days post-coma) she was reported: "dazed all night, did not sleep well"; on the 7th night: "unco-operative". On her 9th hospital day she was seen by the/

the consultant psychiatrist and was transferred to Royal Edinburgh Hospital on the 3rd January, 1969 (7 days post-coma) for psychiatric in-patient care.

After recovery from coma it was noted that her short term memory span had decreased to about 10 seconds, suggesting some brain damage, therefore a repeat EEG and full psychometric testing were carried out at the Royal Edinburgh Hospital.

Her psychometric testing revealed that she scored at the defective level on verbal intelligence tests and showed some aphasia. Her immediate memory was normal and had improved in her ability to learn or register new material but her memory for personal and current information and orientation was poor.

CASE HISTORY No. 17 (126).

An 18 year old girl had taken unknown quantities of ferrous sulphate and paracetamol tablets on 13th May, 1968. The following day she was unwell and vomited, but by 24 hours after drug ingestion she felt better. Thirty six hours after drug ingestion she became unconscious and was admitted to the Regional Poisoning Treatment Centre, Edinburgh.

Course in the Hospital:-

On admission to the ward she was pale and unconscious but responded vigorously to painful stimulation of her sternum with the knuckles. Her pulse was 140 per minute and pupils normal. Her blood glucose level was reported to be extremely low and blood iron concentration was 90 microgrammes percent. She was/

was treated with desferrioxamine mesylate.

Two hours after admission (30 hours after drug ingestion) she had haematemesis and three litres of blood was aspirated through the stomach tube. However, she improved over the next three hours and was fully conscious five hours after admission but was agitated and complained of backache. Six hours after admission (43 hours after drug ingestion) her blood pressure again fell and the question of gastric surgery to control haematemesis was considered but as her prothrombin time was increased to 5 times that of control, it could not be carried out. Seven hours after admission she had a cardiac arrest, but was resuscitated. Her blood pressure continued to fall despite all measures and she had a second cardiac arrest and once again was resuscitated. Clinically she was deeply unconscious and totally unresponsive to any stimuli. She was on assisted ventilation.

Her EEG record eight hours after admission was completely isoelectric (Grade VII) and showed no sign of cerebral electrical activity, even after painful stimulation. Clinically her condition remained unchanged. Her blood pressure was unobtainable and temperature not recorded.

Nine hours after admission (46 hours after drug ingestion) she had a third cardiac arrest and external cardiac massage was started. Her EEG record was completely isoelectric and showed no sign of activity even when recording was done on maximum gains (20 $\mu\text{V}/\text{cm}$) and after stimulation. Clinically she was deeply comatose and totally unresponsive to all stimuli. She had marked hypotension and was on a respirator. External cardiac massage/

massage was continued and the opinion of a consultant cardiologist sought.

In view of her clinical condition, including marked hypotension, severe haematemesis, three cardiac arrests, assisted ventilation, failure of return of spontaneous cardiac rhythm and a completely isoelectric EEG record, she was pronounced dead in consultation with the Consultant Physician, Consultant Cardiologist and Dr. Ian Oswald. She was a donor for the first lung transplant operation carried out by the Edinburgh surgical team. (Matthew et al., 1968).

CASE HISTORY No. 18 (123/119/CM)/

CASE HISTORY NO. 18 (123/119/CM).

A sixteen year old girl was admitted to the Regional Poisoning Treatment Centre, Royal Infirmary of Edinburgh at 02.30 hours, three and a half hours after the ingestion of 40 tablets (800 mg.) of fenfluramine. She was agitated, anxious, uncooperative, flushed, sweating and slightly obese. Blood pressure was 120/80 mm. Hg., pulse 134 per minute, regular in time and force, temperature 37.2°C and respirations 22 per minute. She was fully conscious with dilated pupils, unreactive to light; there was a rotary nystagmus, and the deep tendon reflexes were brisk and symmetrical. A pronounced feature was a continuous tremor of the lower jaw with chattering of the teeth. Stomach washout was performed with return of tablet material.

Continuous EEG monitoring was started three hours after admission and her EEG record revealed Grade I EEG. At 09.00 hours she was hyperventilating and the widely dilated pupils reacted sluggishly to light. Arterial blood-gas showed a respiratory alkalosis - serum pH 7.55, standard bicarbonate 25 meq. per litre, and PCO_2 21 mm.Hg. Blood-glucose was 59 mg./100 ml.

A forced acid diuresis was started at 13.00 hours. She was given a total of three litres of fluid including 70 meq. of ammonium ion intravenously during four hours. At the end of this time she was ventilating normally, was less agitated, and the tremor of the lower jaw was absent. The arterial blood-gas now showed/

a pH of 7.32, standard bicarbonate 16.6 meq., per litre, and PCO_2 28.5 mm.Hg.

The further recovery of this patient is discussed in project No. 3 (Patient No. 11).

CASE HISTORY No. 19 (124/120/YM).

A sixteen year old girl was admitted at 22.00 hours, having ingested 30 tablets (600 mg.) of fenfluramine two and a half hours earlier. She complained of a burning sensation in her epigastrium, of feeling hot all over, and of some blurring of vision.

She was fully conscious and cooperative but flushed and warm. Her blood pressure was 130/90 mm.Hg., pulse 130 per minute, regular in time and force, respiratory rate 30 per minute and temperature 39.0°C . The pupils were widely dilated and failed to react to light. A rotary nystagmus, and a weakness of the left lateral rectus muscle were present. There was a continuous tremor of the lower jaw with chattering of teeth. Generalised hyperreflexia and ankle clonus were present. The blood-gases after stomach washout revealed a pH of 7.35, a PCO_2 of 43 mm.Hg. and a standard bicarbonate of 22 meq. per litre.

Continuous EEG monitoring was started two hours after admission. Her record revealed Grade I EEG changes and contained continuous muscle artefact in all channels, superimposed on the EEG traces.

Next morning at 09.00 hours her vision had cleared but her other symptoms were unchanged. The pupils were still dilated and/

and unresponsive to light and the rotary nystagmus remained. There was no weakness of the left lateral rectus and limb reflexes were normal. The next day she was symptom free, the pupils were dilated but reacting to light. Further studies with this patient are described in project No. 3 (Patient No.12).

CASE HISTORY No. 20 (125/121/M).

This sixteen year old girl was admitted at 22.00 hours having ingested 20 tablets (400 mg.) of fenfluramine two and a half hours prior to admission, in company with another patient (Case No. 124). She complained of a "ball of fire" in her epigastrium and of feeling hot all over.

She was conscious, cooperative, flushed and warm. Her pulse was 108 per minute, regular in time and force, blood pressure 130/70 mm.Hg., temperature 37.6°C and respiratory rate 26 per minute. The pupils were widely dilated and unresponsive to light and there was a significant rotary nystagmus. The deep tendon reflexes were brisk and symmetrical. Stomach washout was performed with a good return.

Continuous EEG monitoring was started three hours after admission and her record revealed Grade I EEG changes. Next morning at 09.00 hours she complained of feeling tired, said her legs felt like jelly and that she had a burning feeling all over. Her pupils were dilated and slightly responsive to light. There was no nystagmus. Serum-fenfluramine 14 hours after ingestion was 0.163 µg. per ml. On day 3 the pupils were dilated and responding to light.

D I S C U S S I O N

As outlined in the introduction previous investigations of drug induced coma (Wulff, 1950; Mantz et al., 1965; Wallace and Allen, 1968) have described the slowing and general flattening of the electroencephalogram in acute drug intoxication but these reports dealt with only small series of comas compared with the present study and did not employ continuous EEG monitoring. The results of the present investigation offer strong confirmation of the few previous case reports (Warter et al., 1963; Bird and Plum, 1968) that flat EEG records in cases of drug intoxication are quite compatible with eventual recovery. The use of term "flat" record in previous reports (Mellerio, 1964; Wallace and Allen, 1968) is difficult to interpret owing to the use of only short periods of EEG sampling (Mantz et al., 1965). The continuous EEG monitoring technique employed in this study confirmed the presence of very prolonged periods of isoelectric record in the cases reported here. In the investigations mentioned above, the recording sensitivity used was only that customary in routine clinical recordings and it was this that was used in determining electrocerebral silence. The use of stimulation and increased amplification in the present study made it possible to show that the EEG records were completely isoelectric.

EEG monitoring proved at times superior to clinical observation and of great help in assessing a change in the condition of those patients (Case Histories No. 1 and 4) who were/

deeply comatose and unresponsive to all stimuli.

The EEG grades V-VII were associated with deep coma and could not be distinguished clinically whereas the EEG provided evidence of beginning improvement from, for example, Grade VII to Grade V. In this respect the present investigation confirms the findings of Sament and Huott (1969). An improvement in the electrical activity always preceded the clinical signs of improvement. For many hours a patient may not show any notable change in the clinical condition, whereas EEG activity will continue to show steady improvement (Haider et al., 1968). This is also illustrated by case histories 1, 3, 5, 10, 11, 12 and 13). Another area in which EEG monitoring proved to be useful, was in the assessment of the effectiveness of some active regime adopted (case histories No.3 and 13). Other investigators (Brazier et al., 1945; Swank and Foley, 1948; Bickford, 1950; Courtin et al., 1950; Kiersey et al., 1951; Sament and Huott, 1969), have shown that the EEG is the best single measure of the depth of barbiturate narcosis and that it is superior, in this respect, to clinical or biochemical testing. These studies were performed experimentally on animals and also during thiopentone anaesthesia in man. The present study allows the same conclusions for acute drug intoxication in man.

Nitrazepam proved remarkable in that it produced least change of consciousness, and only minor EEG abnormalities were seen even with large overdose (40 tablets, 200 mg. - case history No. 6)/

Whereas a similar quantity of other hypnotics (40 tabs. of methyprylon - case history No.9; 40 tablets of Mandrax - case history No. 5) resulted in deep coma and severe EEG abnormalities.

Non-parametric tests were able to establish significant correlations between the EEG grades of coma and the age, clinical assessment of depth of coma, body temperature, duration of unconsciousness, and blood drug levels. As far as is known no previous investigation of these inter-relationships has been reported. If the EEG is to be used to monitor coma it is plain that body temperature especially, must always be taken into account.

The value of the EEG for monitoring coma is abundantly clear but its routine clinical use must be admitted to have limitations because it throws heavy demands on skilled labour and involves complex and bulky equipment producing miles and miles of recorded paper. It must be thought too expensive and intricate for use in routine monitoring. However the present study suggests that a simple and less expensive device for continuous monitoring such as the cerebral function monitor described by Maynard et al., (1969), could be a valuable aid to the clinician in making decisions about the treatment of comatose patients and in assessing the probability of survival.

V. RESEARCH PROJECT NO. 3.

V. A. TITLE:- Follow up study of late brain recovery of patients after they have made a clinical recovery from acute drug poisoning.

V.B. Introduction:-

Persons taking very large amounts of barbiturates are liable to convulsions, delirium, insomnia, and other symptoms if their drugs are suddenly withdrawn. These features occur especially in the first week but can continue for two weeks (Wulff, 1959; Fraser et al., 1954).

Barbiturates suppress REM sleep, not merely reducing its duration and delaying its onset, but reducing also its intensity, as judged by a significant reduction in the profusion of accompanying rapid eye movements (Oswald et al., 1963; Baekland, 1967). The profusion of rapid eye movements is correlated with the degree of "activity" of the accompanying dream (Dement and Wolpert, 1958; Berger and Oswald, 1962).

Withdrawal of amylobarbitone sodium following its regular administration for eighteen consecutive nights led to rebound abnormalities (Oswald and Priest, 1965). Despite the short period of exposure to the drug, the abnormalities did not completely subside till the sixth week after withdrawal. The same authors reported similar findings in a parallel study of the non-barbiturate hypnotic, nitrazepam. In each case withdrawal of the drug was accompanied by unpleasant subjective effects/

effects, in nightmares. Le Gassioke et al., (1965) reported vivid nightmares provoked by withdrawal of tranlycypromine from an addict. Withdrawal of all these drugs was reported to have caused a very early onset and an early-night excess of REM sleep. Kales and Jacobson (1967) have observed similar nightmare induction by withdrawal of pentobarbitone and also withdrawal of methypylon. Freeman et al., (1965) reported that meprobamate in clinical doses suppresses REM sleep and a rebound effect on withdrawal of the drug has also been described (Oswald et al., 1968; Evans and Lewis, 1968).

Kales et al., (1968) reported sleep patterns of a sodium pentobarbitone addict before and after drug withdrawal. While on the drug, the percentage of REM sleep was low (10%) and stage 4 sleep was absent. As the drug was withdrawn, percentage stage REM increased to levels of 30-40% and the patient reported a number of dreams, several being nightmares. Four months after discharge, he was reported to have a normal percentage of stage REM and 4.

It is known now that the hypnotic drugs depress REM (dreaming) sleep, and that, after several nights, some tolerance develops with a return towards normal REM sleep values despite continuation of the drugs (Oswald and Priest, 1965; Kales et al., 1968; Evans et al., 1968). When the drug is stopped the characteristic "rebound" increase in REM sleep is observed. At this time eye movements are very active and the subjects frequently report frightening dreams.

Other drugs known to cause abnormalities in sleep patterns/

patterns are amphetamines (Rechtschaffen and Maron, 1964), methylphenidate (Baekeland, 1966) and diethylpropion (Oswald et al., 1969). When patients addicted to dexamphetamine, dexamphetamine-barbiturate mixtures, or phenmetrazine, continued to take their accustomed drugs, the proportion of whole-night REM sleep was normal. When the drug was withdrawn abnormalities appeared. When the drug was restored, these abnormalities of brain function disappeared, and reappeared when the drug was withdrawn once again. The abnormalities included excess whole-night REM sleep, with a particular excess in the early part of the night, and abnormally early onset of REM sleep (Oswald and Thacore, 1963). Up to two months elapsed before these abnormalities resolved. Anti-obesity drugs such as diethylpropion and fenfluramine were compared for their effect on sleep (Oswald et al., 1968). Diethylpropion caused three principal abnormalities of sleep; frequent awakenings, suppression and delay to REM sleep, and frequent shifts into and increased time in stage 1. Fenfluramine caused neither of the first two abnormalities, but did cause frequent shifts into stage 1 sleep and increase of time spent in it.

All these studies are concerned with the sleep patterns of either normal healthy volunteers who were given relatively small doses of drug or patients who had been taking the maximum prescribed therapeutic dose of hypnotics over a long period, and the present literature lacks any systematic study of sleep patterns of patients after acute drug poisoning. However, some clinical observations on the sleep of patients of barbiturate intoxication have been made. Prolonged post-coma insomnia is not rare. Wulff (1950) noted persistent wakefulness after drug/

overdose coma in a study of 85 cases of barbiturate withdrawal syndrome. In 21 cases decreased or absent sleep, amounting to four hours or less in 36 of the 140 nights was reported. The third, fourth and fifth nights were the most sleepless in two thirds of the cases.

Bird et al., (1968) reported pronounced post-coma insomnia in six of seven cases of drug poisoning but only one patient's post-coma EEG sleep was recorded which revealed an increase in slow wave sleep without an increase in REM sleep. The same authors also studied sleep patterns of three cats before and after sodium pentobarbitone-induced coma, no post-coma insomnia was observed, and the cats had increased slow wave sleep, but no decrease in REM sleep. REM sleep time was reported to be less than control levels in the immediate post-coma period, then gradually increased to, but did not exceed, pre-coma levels. Some authors (Bird and Plum, 1968) reported recovery of a patient from barbiturate overdose coma who did not sleep at all for two and one-half days post-coma and had no significant periods of sleep until the eleventh hospital day. However no EEG sleep recording was done in this case.

Some of the patients studied in Project No. 2 during their follow-up mentioned poor sleep and nightmares in the weeks after coma. Therefore a follow-up study of sleep recovery of some of these patients after they had made a clinical recovery from acute drug poisoning was undertaken.

V.C. METHODS AND MATERIAL:-

Selected/

Selected patients were drawn from a thousand poisoned patients admitted in 1969 to the Regional Poisoning Treatment Centre, Royal Infirmary of Edinburgh under the care of Dr. H.J. Matthew. They were later transferred to a psychiatric ward of the Royal Edinburgh Hospital where the patient's individual needs caused variability in the extent of the studies.

The patient prepared for sleep each night and had small silver disc electrodes attached above and below each outer canthus, to the scalp, and over the submental muscles. Fine wires from these electrodes, gathered together at the scalp, made possible recording of electroencephalogram (EEG), eye movements and muscle tension (EMG) at a paper speed of 15 mm/second. The patient then slept in a small room within the ward, the EEG machine being in an adjacent room.

Approximately a third of a mile of recording paper (64 miles in all) was obtained each night and this was scored page by page according to standard criteria (Rechtschaffen and Kales, 1968). Among scores obtained were: total time asleep, the number and duration of awakenings and the number of shifts to and duration of the various stages of sleep, namely stage 1 (drowsiness), 2, 3 and 4 (largest slow EEG waves) of orthodox (NREM) sleep, and paradoxical (REM or rapid eye movement) sleep. Particular reference is made below to the percentage of sleep spent as REM sleep. In addition, since a variety of previous studies (Oswald and Priest, 1965; Oswald et al., 1968) have indicated that the first two hours of sleep is an especially informative/

informative period, reference is made to a measure of spontaneous restlessness in this time, namely the total number of shifts from any other stage of sleep to stage 1 (drowsiness) or wakefulness between first falling asleep (onset of first sleep spindles of stage 2) and the accumulation of a total of 2 hours of sleep, and also to the duration of REM sleep in this two hours. The latter duration does not normally exceed 35 minutes in young people, in whom also the delay between the first sleep onset and first REM sleep normally exceeds 45 minutes (Oswald, 1968). In addition I took particular note of the presence and eventual disappearance of EEG fast activity of the type often called "barbiturate fast" which, however, also is caused by various other drugs, and to this end recordings were made without the use of high frequency filters.

PATIENT 1: (72/110/ES)

A woman of 47 was admitted to the Regional Poisoning Treatment Centre on 21st March, 1969, after having taken an overdose of Mandrax (about 40 tablets). She had been taking one or two "Mandrax" (methaqualone 250 mg. with diphenhydramine 25 mg.) nightly for three months. On admission to the ward she was deeply unconscious and unresponsive except to maximal stimulation. Continuous EEG monitoring was started soon after admission to the ward and continued throughout her period of unconsciousness and for some time after. Her clinical course in the hospital and EEG changes have already been described in Project 2 (see case history No. 5). She regained consciousness after 105 hours and was seen by Dr. Ian Oswald, the consultant psychiatrist, who transferred her to the North Wing of the Royal Edinburgh Hospital for psychiatric in-patient care, where her all-night sleep studies were done. No physical treatments were employed during the period of study outlined below.

In the subsequent two days she developed a mild delirium with visual hallucinations and disorientation which did not wholly clear till the 11th day. No drugs were given. Her all-night sleep was recorded on the 5th post-overdose night, but on this, and the next three nights, it was extremely broken and irregular, consisting on nights 5, 6 and 7 only periods of stage 1 and of REM sleep, each briefly intruding directly from wakefulness and often for only a few seconds at a time. On the 5th night recording lasted for eight hours and five minutes, but she slept for only 12 minutes. Her record (Fig. 95) consisted of periods/

SLEEP AFTER MANDRAX OVERDOSE.

(PATIENT 1)

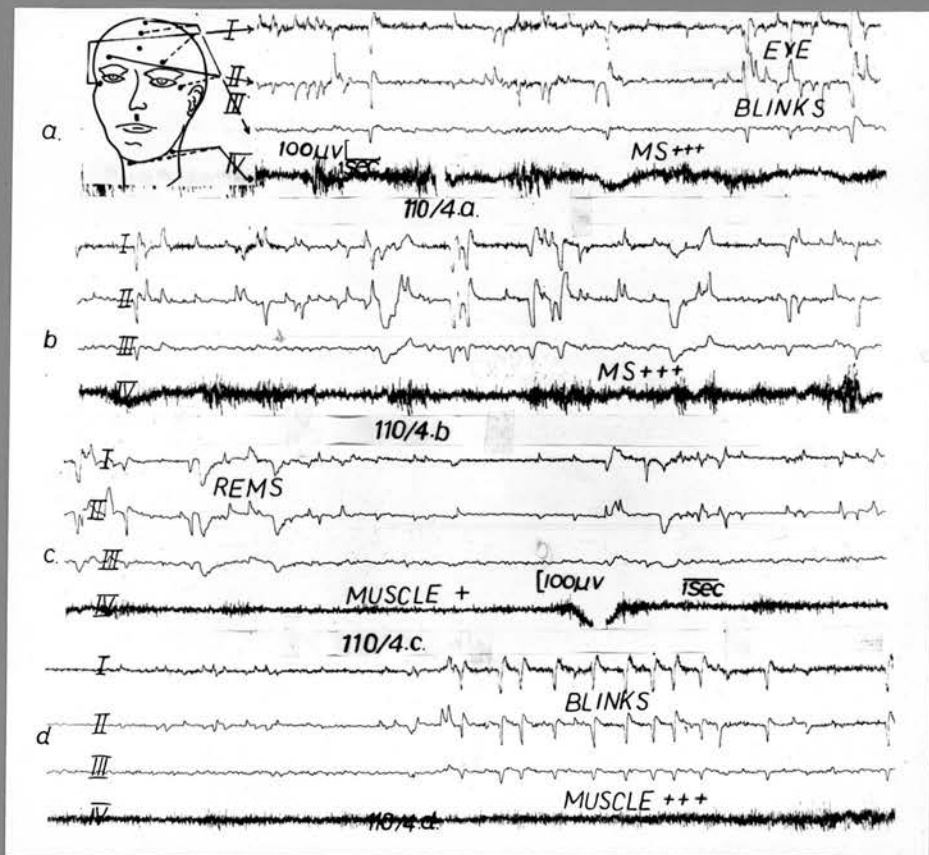


Figure : 95

On the fifth post-overdose night she had five minutes of stage 2 sleep but she began her night with REM sleep. These four excerpts are continuous. The top excerpt indicates that the patient is awake, with eye blinks and increased muscle tone (MS). The second excerpt contains rapid eye movements and low voltage 3-4 cps EEG waves. These features suggest REM sleep yet muscle tone remains increased. The third excerpt shows rapid eye movements of the appearance usual in REM sleep and decreased muscle tone with low voltage EEG slow waves. This picture continues into the fourth excerpt, in the middle of which waking eye blinks re-appear and muscle tone is increased, no rolling eye movements of stage 1 sleep are visible. MS = Muscle tone.

periods of wakefulness with eye blinks, stage 1 with alpha rhythm and REM sleep with rapid eye movements and low voltage EEG. Muscle tone was quite variable but ~~never absent~~, and therefore, at times, a distinction between REMS of REM sleep and blinks or REM of wakefulness became difficult. Moreover as the REMS mixed with blinks occupied 20-50% of an epoch the scoring of the epoch was almost impossible. She began her night's sleep with what was interpreted as REM sleep but there were no stages 2, 3 or 4. In the morning she was confused and disorientated. Her blood methaqualone level was 3.3 mg.%.

On the 6th post-overdose night she slept for 69 minutes. Her first sleep was REM sleep and her EEG record (Fig. 96) still contained a mixture of periods of low voltage slow wave EEG with REMS like those of REM sleep, on the one hand, and obvious wakefulness on the other. There were no stages 2, 3 or 4. She was fearful of being left alone, and wanted the light left burning. She took the central heating pipes for some sort of device to kill her after I had left the room. In the middle of night she shouted for help and asked for talcum powder which she started sprinkling on the blankets saying that she wanted to die smelling nice. In the early hours of the morning she was seeing things crawling toward her and these changed colour.

On the 7th night she slept for 139 minutes but there was no stage 2, 3 or 4. She again began her night's sleep with REM sleep (Fig. 97) and shifted between stage 1, REM ~~period~~ sleep/

SLEEP AFTER MANDRAX OVERDOSE.

PATIENT 1

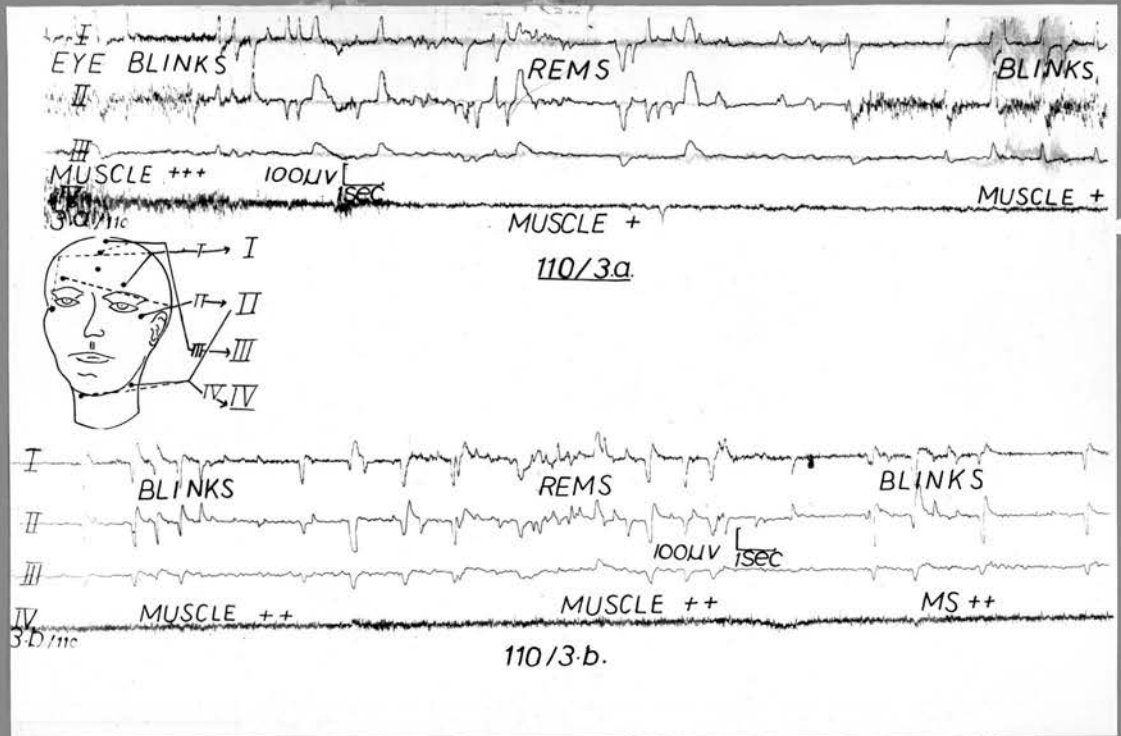


Figure : 96

The 6th night after the overdose. These two continuous excerpts illustrate the transition from wakefulness to what is probably REM sleep and again to wakefulness. The upper excerpt shows wakefulness with eye blinks and increased muscle tone passing directly into a period of rapid eye movements and decreased muscle tone. Seven to eight seconds later eye blinks re-appear and muscle tone is increased. The second excerpt shows obvious wakefulness with eye blinks and increased muscle tone passing into a period in which low voltage slow EEG waves accompanying rapid eye movements of the appearance seen in REM sleep, but muscle tone remains unchanged. Five seconds later eye blinks are prominent, muscle tone shows no change and the patient must be judged awake. MS = muscle tone.

SLEEP AFTER MANDRAX OVERDOSE.

PATIENT 1

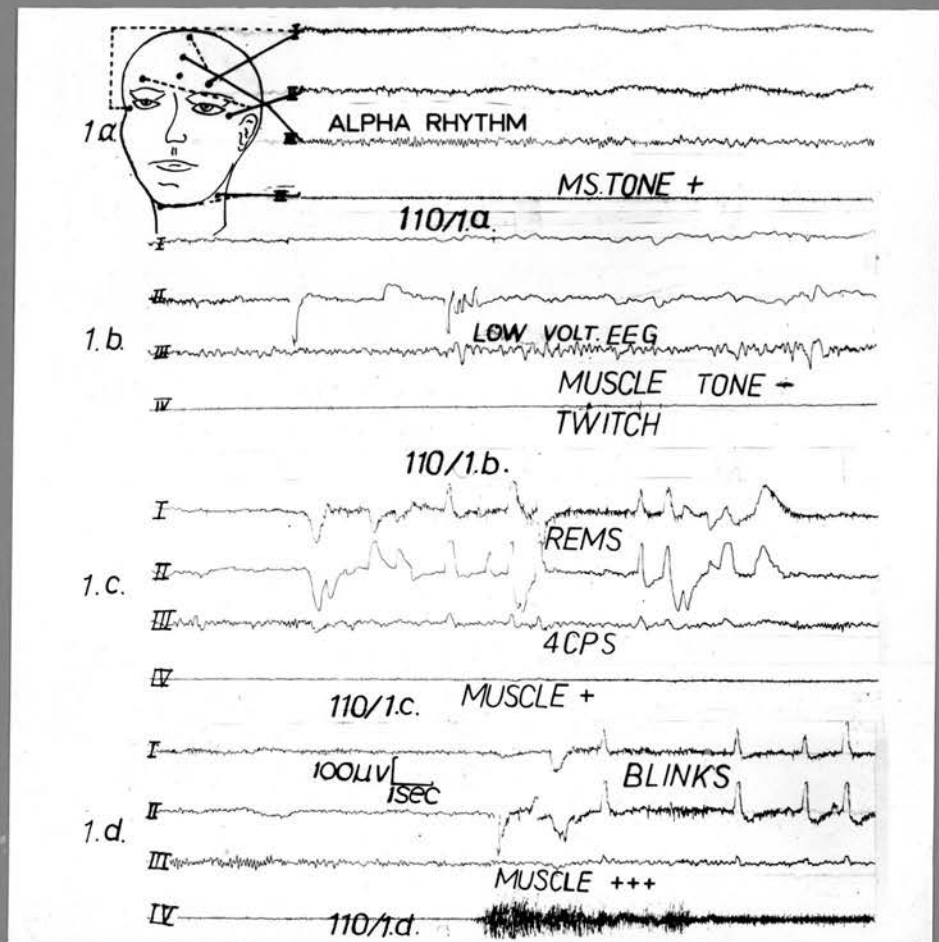


Figure 1: 97

On 7th post-overdose night her sleep consisted of periods of stage 1 and of REM sleep. These excerpts illustrate the transition from wakefulness, with EEG alpha rhythm, through drowsiness with rolling eye movements and loss of alpha rhythm directly into REM sleep with low voltage 3-4 cps EEG waves and rapid eye movements. All the four excerpts are continuous with one another. The third and fourth excerpt show a transition from REM sleep to wakefulness with the return of alpha rhythm, eye blinks and increased muscle potentials.

sleep, and wakefulness. Most of her record consisted of a mixture of REMS and blinks in the same epochs but some of the REM periods were typical. She was hallucinated, and saw smoke around the light bulb, and complained of terrible smells in the room. She firmly believed that she was going to be blown up.

The following night (8th night) for the first time her record (Fig. 98) contained some poor spindles (Stage 2). She slept for 2 hours and 5 minutes. She continued to be hallucinated, disorientated and confused. On this 8th night she had 5 minutes of stage 2 sleep, 53 minutes on the 9th night, and 180 minutes on the 11th, when she slept for just over 5 hours in all. On the 14th night she had 386 minutes of sleep and remained at just over this duration nightly thereafter.

Fig. No. 99 illustrates the broken nature of her sleep. Her intra-sleep restlessness is shown by the increased number of shifts to stage 1 sleep from any other stage of sleep, or to wakefulness. They numbered 39 on the 7th night. With gradual recovery throughout the period of study they dropped to 12 on the 37th night.

The recovery course of her REM sleep is indicated in Fig. 100. On the first four nights her sleep consisted mainly of REM sleep, stage 1 or wakefulness with no stages 2, 3 or 4. On these nights, as already pointed out, scoring of her record according to the standard criteria was almost impossible but an attempt was made, as best could be. The percentages of REM sleep for these nights is, however, shown merely by dots on Fig. 100, which shows high REM sleep percentages on early nights with recovery to normal levels after five weeks. Other abnormalities in/

SLEEP AFTER MANDRAX OVERDOSE.

PATIENT 1.

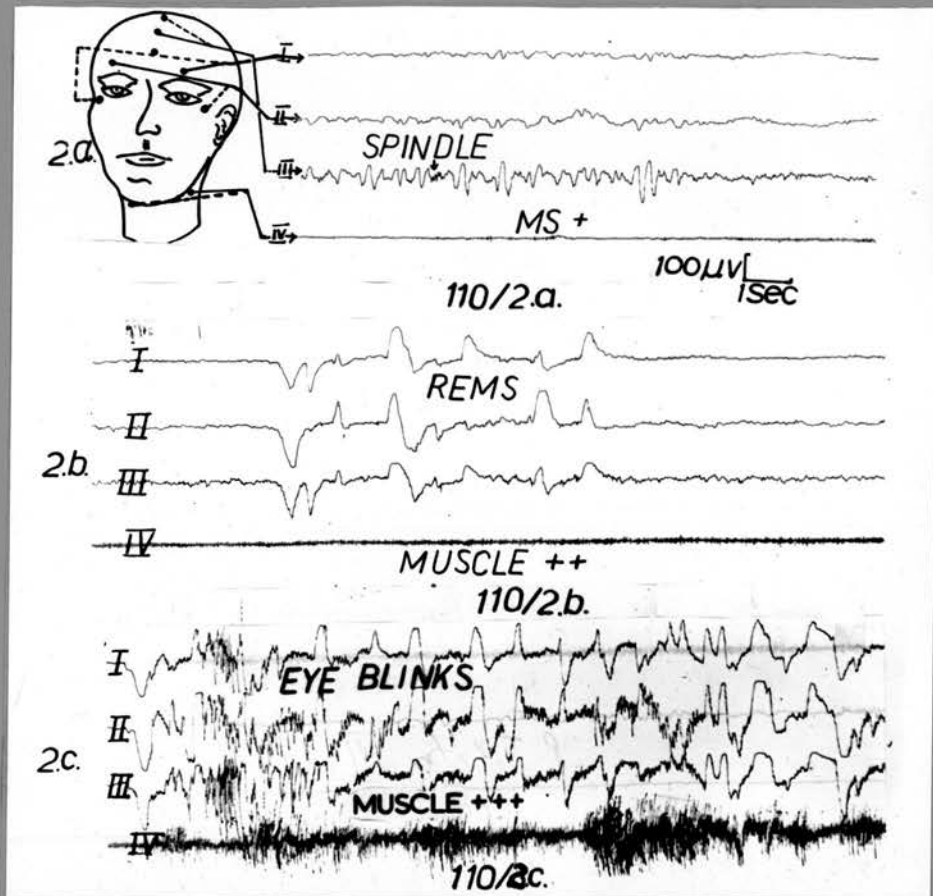


Figure : 98

On 8th post-overdose night the patient passes from Stage 2 with a poor spindle and decreased muscle tone directly on to REM sleep with rapid eye movements, and irregular 5-9 cps EEG waves posteriorly, yet without normal abolition of muscle tone. The three excerpts are continuous. The bottom excerpt shows a series of eye blinks as the patient wakes up. Note muscle tone has greatly increased.

SLEEP AFTER MANDRAX OVERDOSE.

PATIENT 1

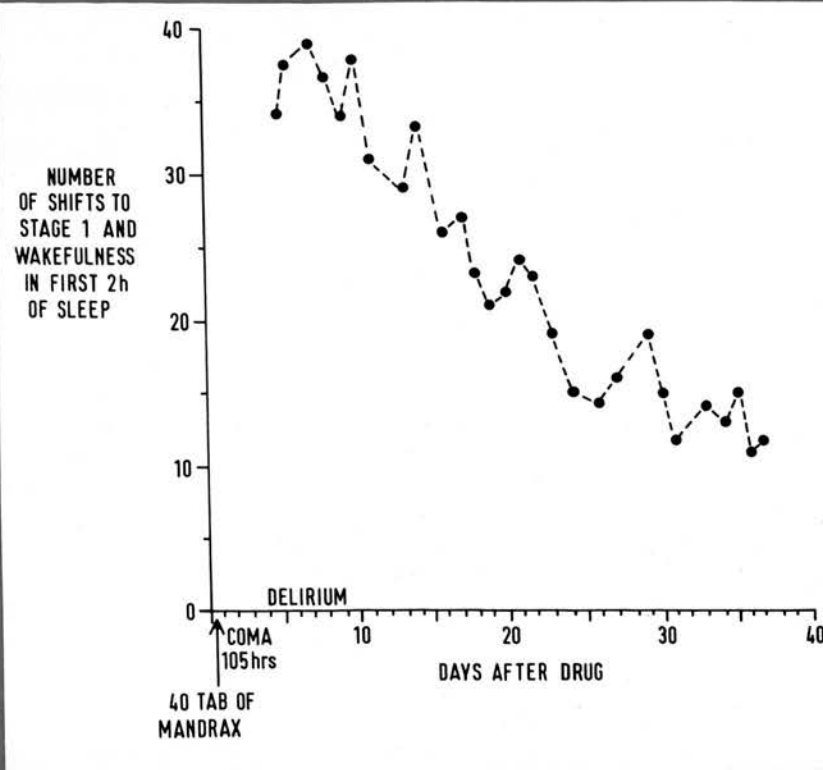


Figure:-99

Restless sleep in the weeks after "Mandrax" poisoning. The number of spontaneous shifts from sleep to wakefulness or to stage 1 sleep before attaining a total of 2 hours of sleep is shown. Restlessness declines towards normal in the month of study. On nights 5, 6 and 10, she slept a total of only 12, 69 and 89 mins. and for these nights the absolute number of shifts in the time asleep is shown, so underestimating the degree of restlessness.

SLEEP AFTER MANDRAX OVERDOSE. PATIENT 1

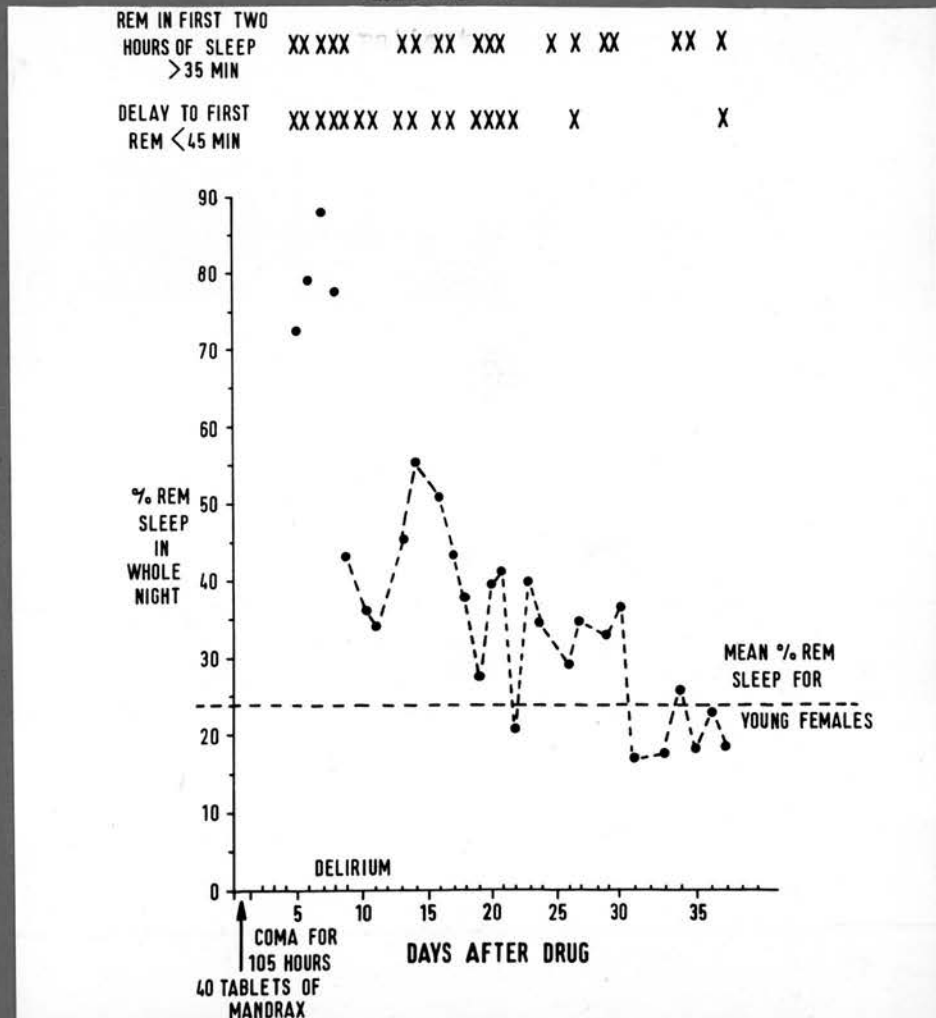


Figure:
100

The percentage of sleep spent as paradoxical (REM) sleep following "Mandrax" poisoning returns to normal a month after overdose, but the excess of early paradoxical sleep and its early onset, indicated by the stars across the top of the figure, indicates that full recovery of this brain function has not occurred in the period during which study was possible.

In the study as a whole the percentage of paradoxical sleep is based on total sleep from sleep onset with first stage 2 EEG sleep spindles. Since on nights 5, 6, 7 and 8 paradoxical sleep appeared in broken episodes without preceding stage 2 sleep, the percentages for those nights are based simply on total sleep, which was mainly paradoxical (REM) sleep with little stage 1. Mean for young women is from Williams et al., (1966).

in her sleep included early onset of REM sleep and its excess in the early part of night. These abnormalities were still present on the 37th night after drug ingestion when she was discharged. Therefore she presumably had not fully recovered to normal by the time of discharge.

Her NREM sleep was also abnormal. Stage 3 sleep was absent until the 16th night (2 per cent) and stage 4 sleep absent until the 31st night. Combined stages 3 and 4 (Fig. 101) rose gradually towards normal in the last three weeks.

Blood methaqualone levels rose to a maximum on the third day (Fig. 102). The curve suggests blood levels would have been negligible by the 7th day but a continuing presence of drug in the brain was revealed by drug-induced EEG fast activity in stage 1 and REM sleep still marked on the 10th day and disappearing on the 16th day.

PATIENT 2:

A 69 year old woman who took about 40 "Mandrax" and who was then unconscious for 2 days had her sleep recorded on the 6th night when, in a total of only 194 minutes of sleep she had 34.5% REM sleep, and woke 18 times before accumulating two hours of sleep. However, she was chiefly of interest on account of the fact that during the night some EEG abnormalities typical of epilepsy were observed in her sleep record. Spikes (Fig. 103) and isolated spike and wave bursts were seen during stages of NREM sleep. She had three prolonged spike-and-wave EEG paroxysms of the type seen in epileptic patients (Fig. 104) each paroxysm lasting over a minute and these were clearly different/

MANDRAX OVERDOSE.
PATIENT 1

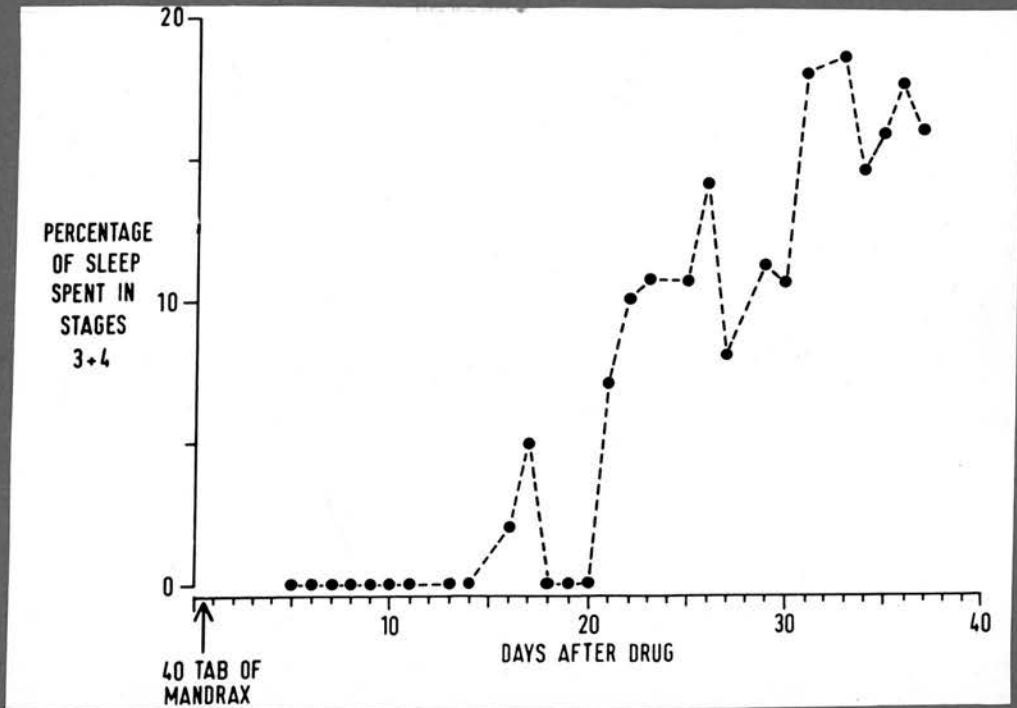


Figure: 101

The EEG slow-wave stages of sleep known as stages 3 and 4 were absent after the poisoning till the sixteenth night after which they recovered normal levels in the subsequent three weeks.

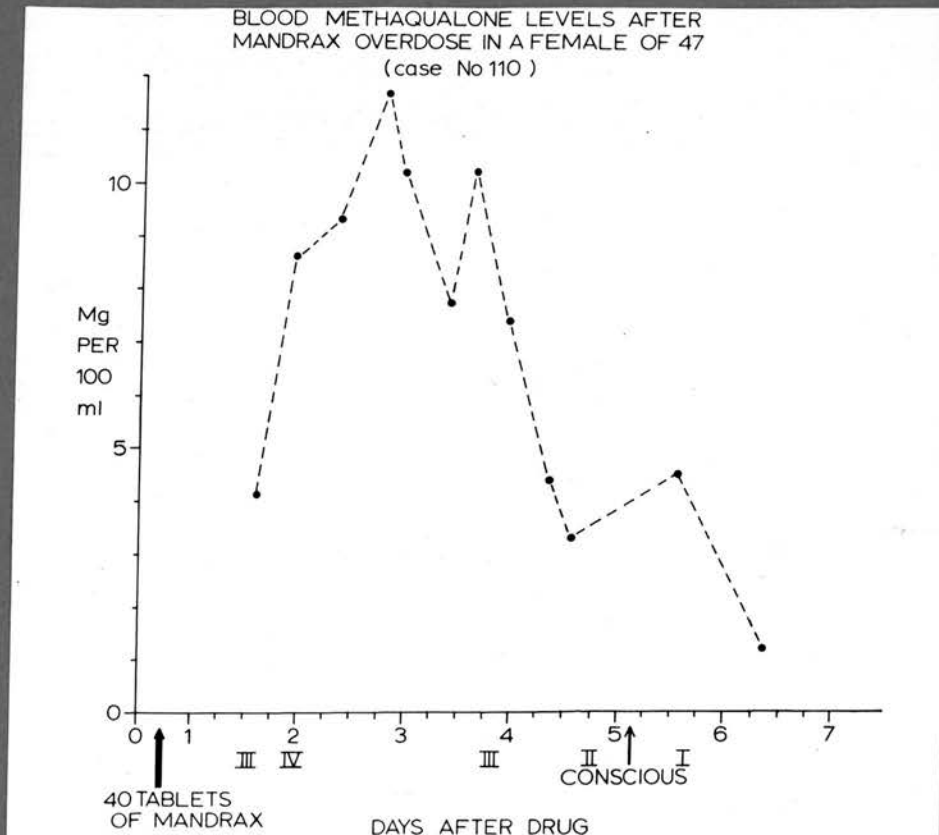


Figure: 102

Blood methaqualone estimations for Patient.

SLEEP AFTER MANDRAX OVERDOSE.

PATIENT 2.

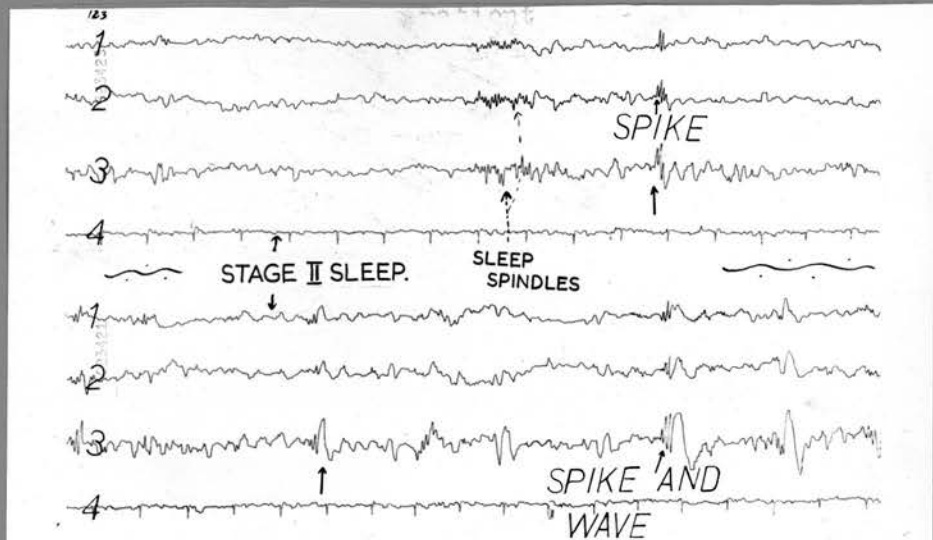


Figure 103:-

Sixth post-overdose night. Top excerpt shows sleep spindles and spikes, the lower excerpt reveals spike-and-wave activity.

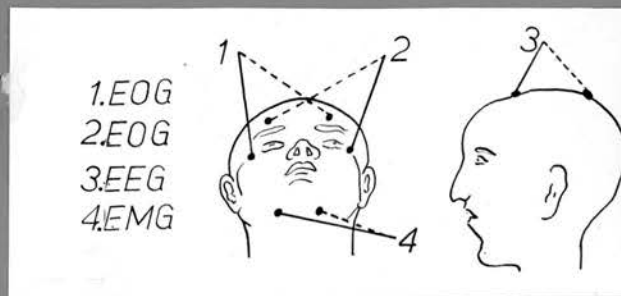
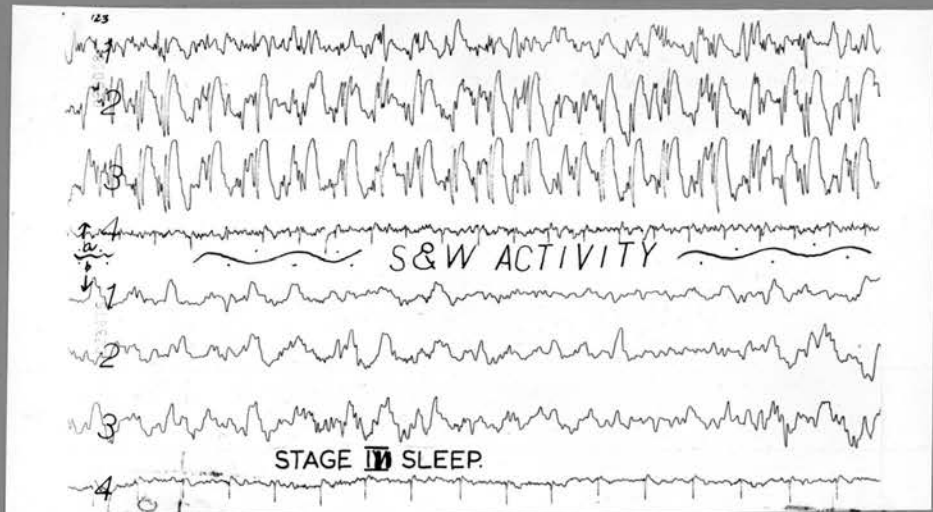


Figure 104:-

Sixth post-overdose night. Top excerpt illustrates generalised spike-and-wave EEG paroxysm typical of epilepsy and is distinctly different from the slow wave activity of NREM sleep (lower excerpt) of the same patient. S + W = spike and wave.

different from the slow waves of NREM sleep. She had no clinical seizures and two weeks later a sleep EEG showed no further paroxysmal features and nor did a waking recording on the 9th day.

PATIENT 3: (117/101/N.R.)

A 36 year old woman was admitted to the Regional Poisoning Treatment Centre, Edinburgh on 1st March, 1969. She had taken 200 mg. tablets of methyprylon hypnotic nightly, but no alcohol, for several months. She was unconscious and totally unresponsive to stimuli.. Continuous EEG monitoring was started two hours after her admission to the ward. Her EEG tracings showed only brief low voltage slow waves in bursts on an otherwise flat background (Grade VI). She regained consciousness after 28 hours of coma and it was learned that she had taken approximately 40 tablets (8000 mg.) of methyprylon about eight hours prior to admission. The clinical course of her illness and EEG changes observed during the period of acute drug poisoning are described in Project No. 2 (see case histories - No. 9).

Forty hours after drug ingestion she was seen by the consultant psychiatrist and transferred to the Royal Edinburgh Hospital for psychiatric in-patient care, under Dr. Ian Oswald, where her all-night sleep recording was done.

She did not sleep at all on either of the next two nights (her EEG was recorded throughout). She became delirious, seeing snakes, gravestones, trees and flowers in the ward, hearing threatening voices and becoming suspicious in her manner.

No/

METHYPRYLON OVERDOSE.

(PATIENT 3)

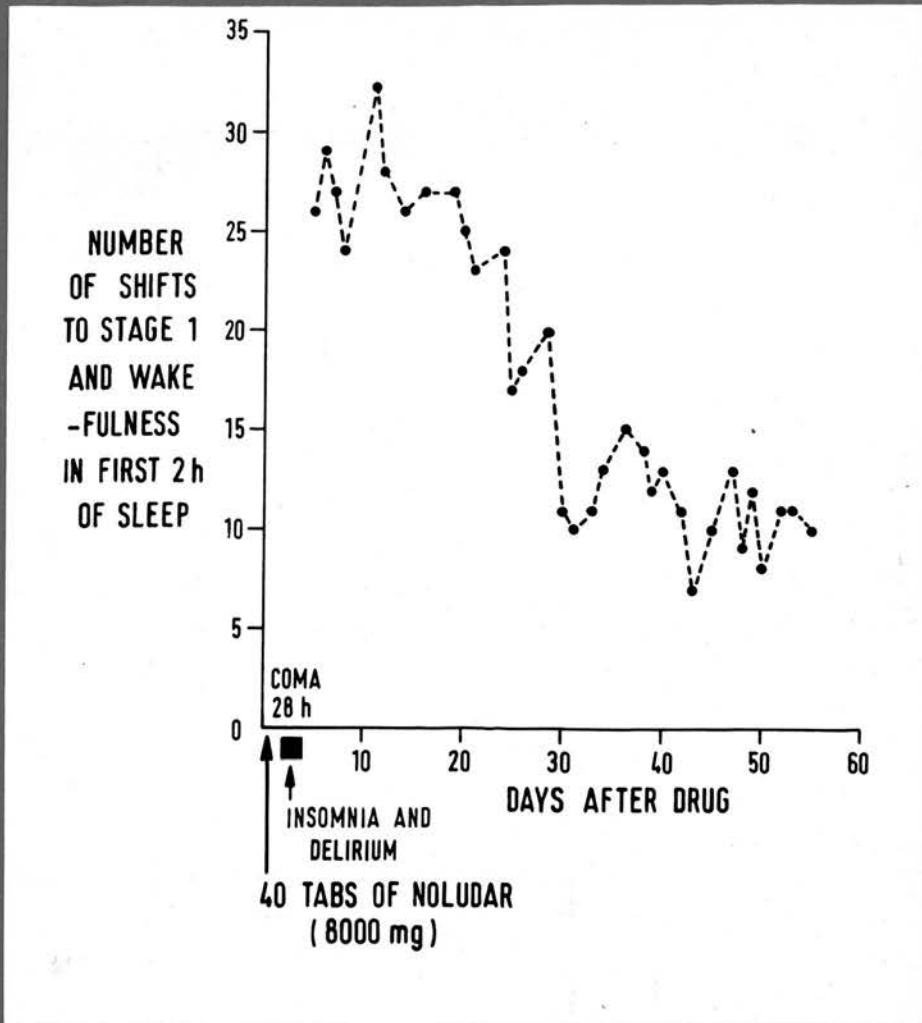


Figure : 105

Restless sleep in the weeks after methyprylon overdose. The number of spontaneous shifts from sleep to wakefulness or stage 1 sleep (drowsiness) to reach a cumulative total of 2 hours of sleep is shown. The rate is very high in the first three weeks and declines towards normal levels over the course of the two months.

SLEEP AFTER METHYPRYLON OVERDOSE.
(PATIENT 3)

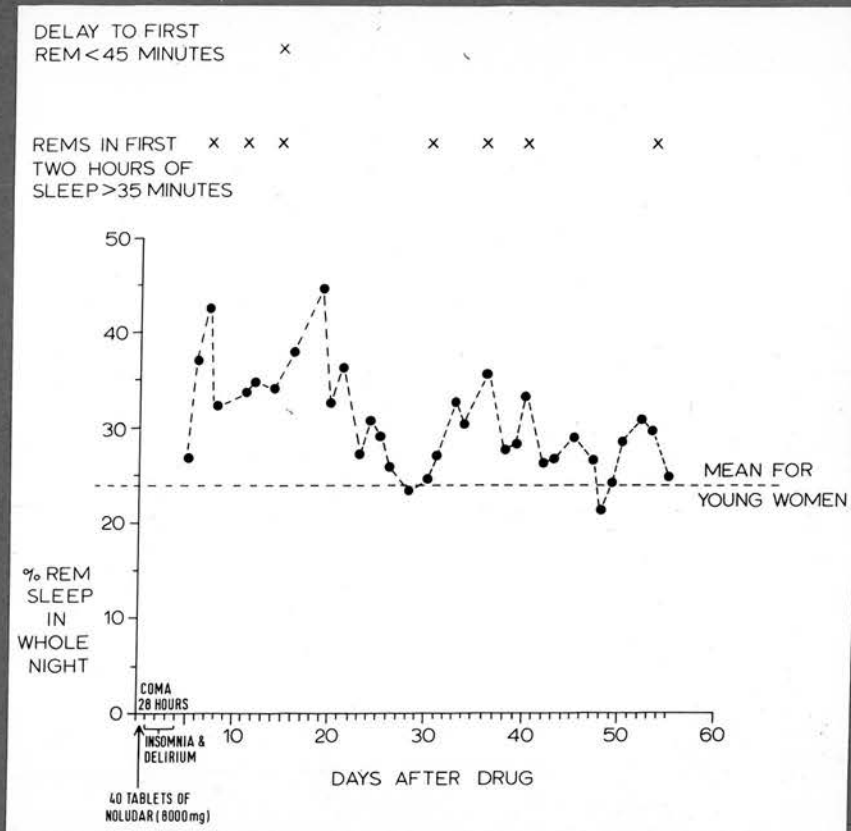


Figure : 106

The percentage of sleep spent as paradoxical (REM) sleep rises to high levels with an irregular decline over the two months. Excess of paradoxical sleep in the first two hours is shown by a star as late as the 52nd night. Drug-induced EEG activity disappeared on the 19th night, when REM sleep percent was also highest. The horizontal line is the mean value for young women (Williams et al., 1966).

SLEEP AFTER METHYPRYLON OVERDOSE

Patient 3, Female, 36 years old.

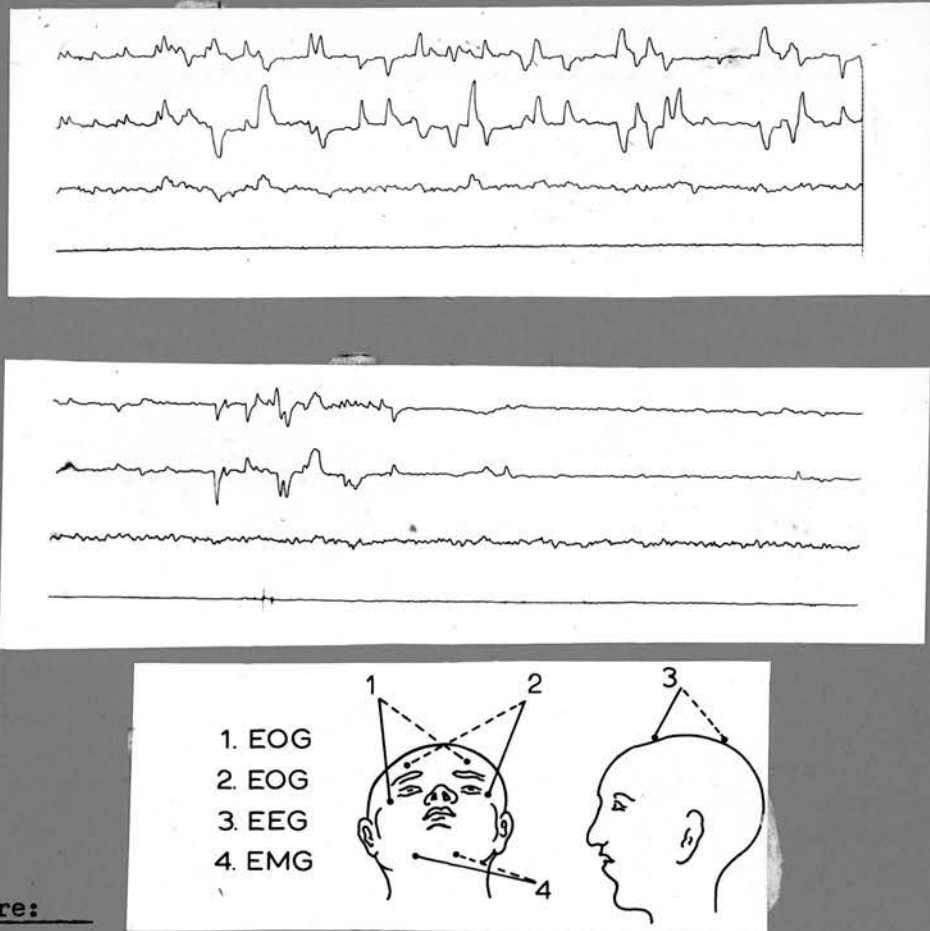


Figure:
107

During REM sleep the eye movements were larger and more profuse about the time of peak REM sleep percentage than when the REM sleep percentage had later returned to normal. Illustration examples are shown from REM periods of patient 3 on (a) the 6th post-overdose night and (b) the 31st night.

BLOOD METHYPRYLON LEVELS AFTER METHYPRYLON
OVERDOSE IN A FEMALE OF 37
(CASE 101)

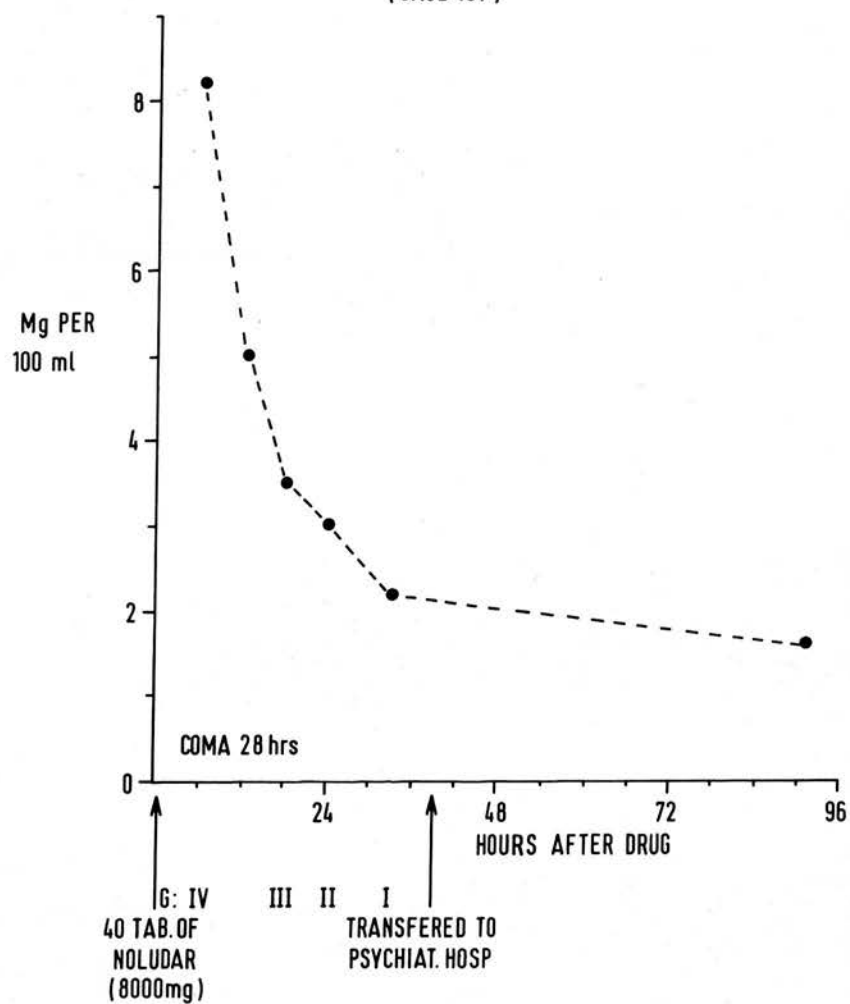


Figure : 108

Blood methyprylon levels after methyprylon overdose.

No attempt was made to record her EEG on the third night but the night nurse reported that the patient had remained awake all night. On the next night she slept for a total of 316 minutes. The sleep, especially in the early night, was punctuated by repeated spontaneous arousals (Fig. 105) indicates that her intra-sleep restlessness was greatest 11 nights after the overdose (with 32 shifts from sleep to stage 1 or wakefulness). She gradually recovered and her sleep patterns returned toward normal over a period of two months.

Her delirium cleared after the first night of sleep and sleep duration increased to 448 minutes by night 8, remaining roughly constant thereafter. The percentage of REM sleep (Fig. 106) was elevated above normal by the 6th recovery night, reaching a maximum of 44.5% on the 19th night. The percentage declined in irregular fashion towards normal values over several weeks but as late as the 53rd night there was an abnormally large amount of REM sleep (40 mins.) in the first two hours of sleep. During REM sleep the eye movements (Fig. 107) were larger and more profuse about the time of peak REM sleep percentage than when the REM sleep percentage had later returned to normal. Her combined stages 3 plus 4, was 5.4, 7.9, 9.8, 10.6, 14.6, 15.3, 16.6, 18.5, and 20.8 percent on nights 5, 7, 14, 19, 21, 24, 26, 28 and 30 respectively.

Drug-induced EEG fast activity, seen in Stage 1 and REM sleep, and drug-accentuated EEG sleep spindles in stage 2, were judged much reduced on the 17th night and absent on the 19th. Blood methyprylon (Fig. 108) in the first six days was 8.2, 5.0, 3.5, 3.0, 2.2 and 1.6 mg. percent respectively.

PATIENT 4: (82/99/EJ)

A nurse of 19 was admitted to the Regional Poisoning Treatment Centre, Edinburgh, at 09.00 hours after having taken about 40 tablets (200 mg.) of nitrazepam eight and a half hours previously. She had been taking two tablets nightly for some months. She was conscious and able to give a history in a quiet, slightly drunken manner.

Continuous EEG monitoring was started soon after admission to the ward. The clinical course of her illness and EEG changes seen during acute drug poisoning are described in Project No. 2 (see case histories-No. 6). She remained conscious throughout the day and was transferred to Royal Edinburgh Hospital for psychiatric in-patient care where sleep studies were carried out.

Her sleep, on the first night was of 462 minutes duration. Drug-induced EEG fast activity at about 18 cps was very prominent in stage 1 and REM sleep and on this first night an enhancement of stage 2 sleep spindles was observed (Fig.109). The second night she slept only 173 minutes, 336 minutes on the third night, and thereafter her total sleep duration varied irregularly between 239 and 495 minutes. EEG drug-induced fast activity disappeared after 9 nights. She was discharged, having received no drugs, after 6 weeks and seen thereafter at the out-patient clinic, from which she was defaulted.

She was re-admitted six weeks later having taken 25 tablets, (125 mg.) of nitrazepam, together with 100 mg. of perphenazine. She was conscious and discharged home the next day from the Poisoning Treatment Centre. At home she "felt I wanted to move my legs all the time" and could not sleep.

SLEEP AFTER NITRAZEPAM OVERDOSE.
Patient 4 - Female, 19 years old.

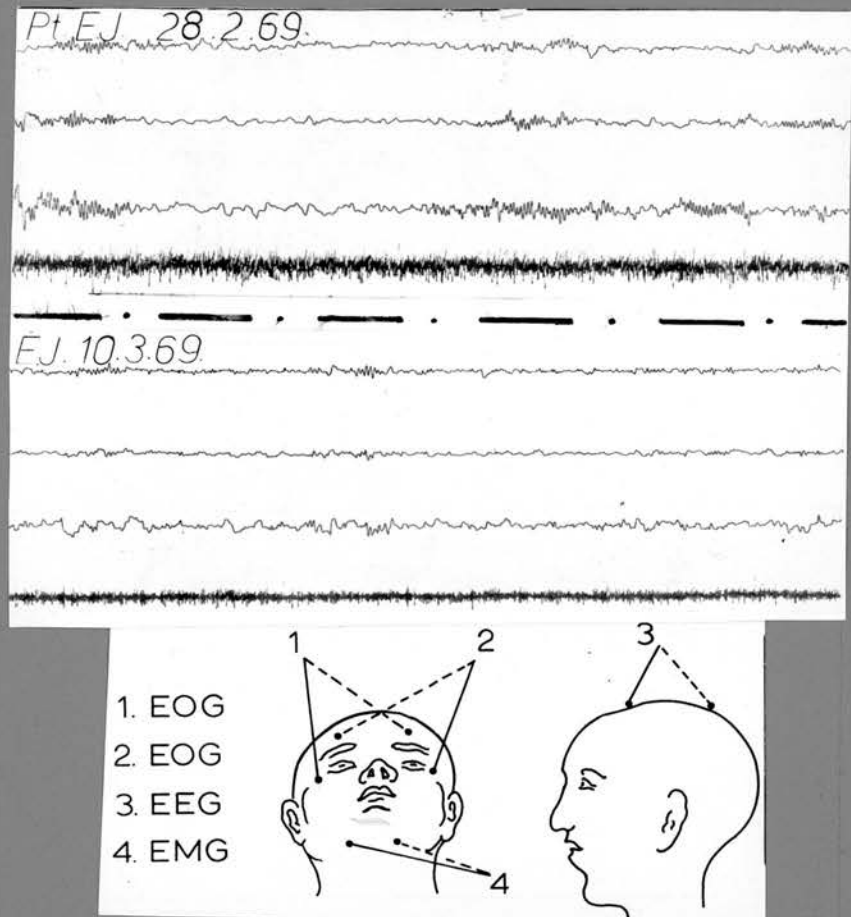


Figure 109

Showing drug-induced accentuation of EEG sleep spindles. The two representative excerpts from the records of patient 4, both illustrate Stage 2 sleep.

The spindles are accentuated three nights after her overdose whereas they appear normal on the 13th night.

Two days after the overdose her family doctor gave her 16 mg. of perphenazine and 400 mg. of pentobarbitone sodium and after another two days 5 mg. of nitrazepam and 25 mg. thioridazine.

She was readmitted to the Royal Edinburgh Hospital as a psychiatric in-patient on the next day when she received no further drugs. Drug-induced EEG fast activity was again prominent till the ninth post-overdose night. On the first night in hospital (the sixth post-overdose) she slept 254 minutes and sleep duration thereafter showed no special trends and varied between 273 and 467 minutes.

In Fig. 110 it may be seen that after each admission intra-sleep restlessness rose to a maximum around the 10th post-overdose night and declined slowly towards normal throughout the following month. REM sleep appears from Fig. 111 to be suppressed by the drug, to reach a maximum around the 10th post-overdose night, and to decline in the subsequent weeks. During REM sleep the eye movements (Fig. 112)) were more profuse and larger about the time of peak REM sleep percentage than when REM sleep percentage had later returned towards normal. Stages 3 and 4 were never absent and rose regularly from 8% on the first night of her admission to around 25-30% of sleep before discharge.

PATIENT 5: S.D.

A 63 year old housewife, who had had meningitis thirty years earlier, after taking a half tablet (2.5 mg.) of nitrazepam nightly for several weeks took about 40 tablets or 200 mg. of the same drug. She was admitted unconscious but responding/

SLEEP AFTER NITRAZEPAM OVERDOSE.
Patient 4, Female - 19 years old.

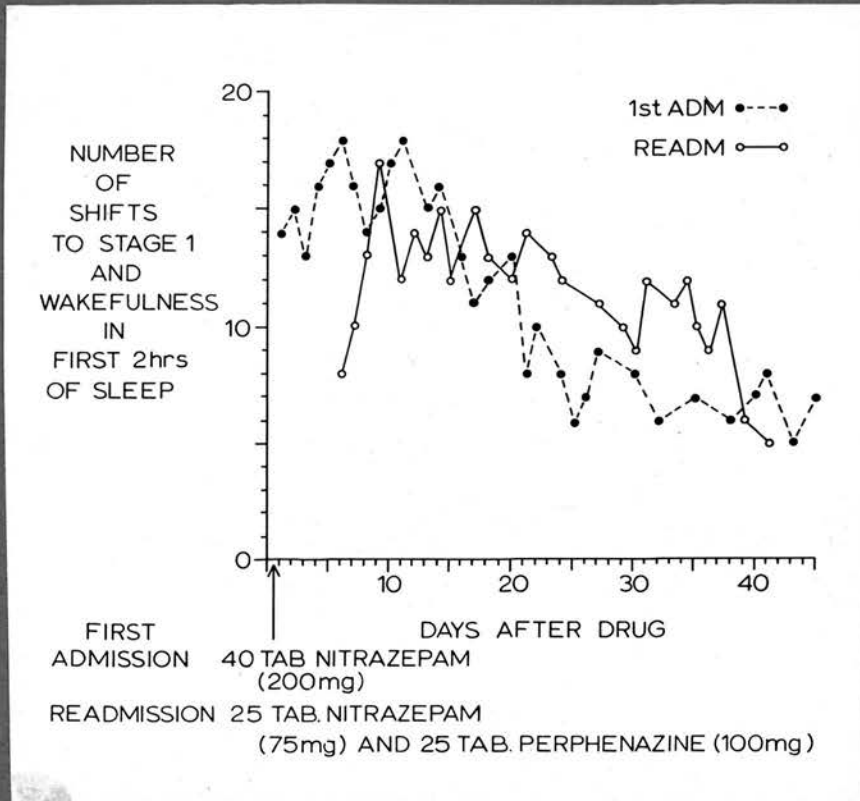


Figure: 110

An index of intra-sleep restlessness following overdose of nitrazepam. It may be specially noted that in each case restlessness is maximal about 10 days post-overdose and declines towards normal over each six weeks. Two months after the last value shown for the readmission study, and without any further drugs, the number of shifts in the first two hours of sleep on two successive nights was only 0 and 2 respectively.

SLEEP AFTER NITRAZEPAM OVERDOSE.

Patient 4, Female, 19 years old.

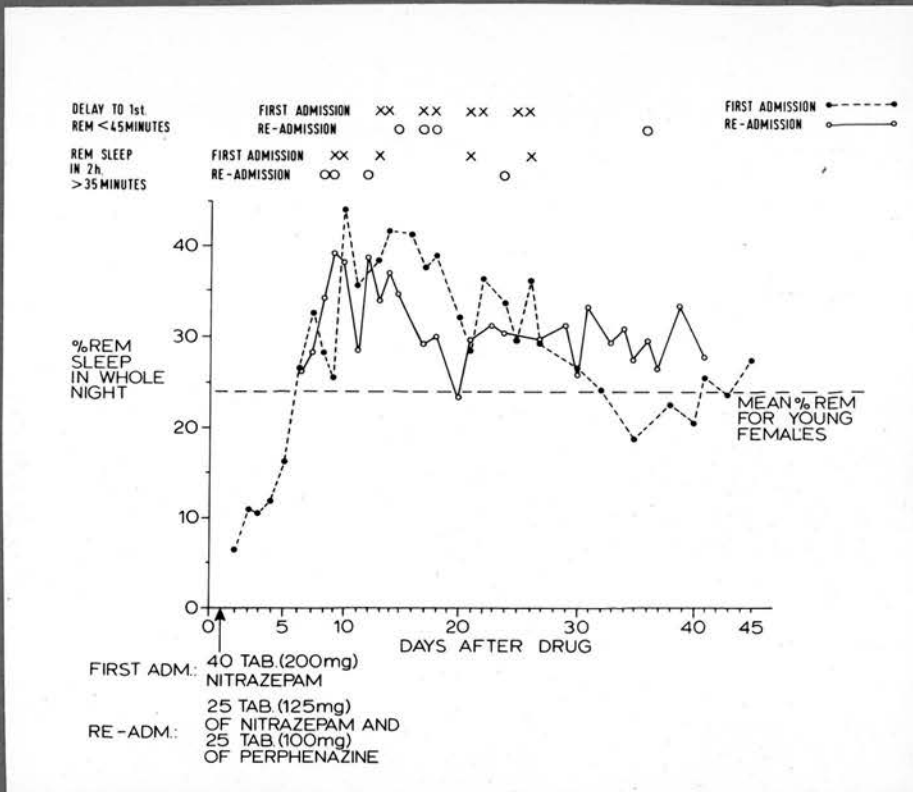


Figure: 111

Paradoxical (REM) sleep is suppressed by the nitrazepam overdose. After each overdose the curves rise to very high levels around the tenth post-overdose day and decline thereafter. Drug-induced EEG fast activity had persisted nine days. As late as the thirty-sixth night after the second overdose one of the limits of normality indicated at the top of the figure, was surpassed by paradoxical (REM) sleep beginning only 39min. from sleep onset.

SLEEP AFTER NITRAZEPAM OVERDOSE.
Patient 4 - Female, 19 years old.

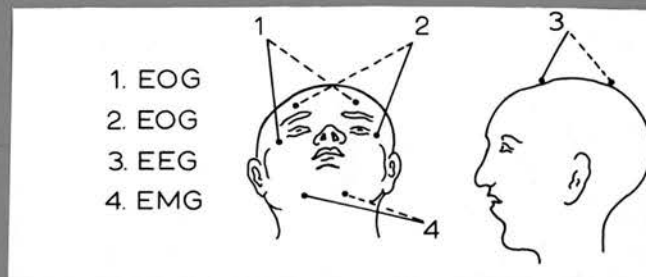
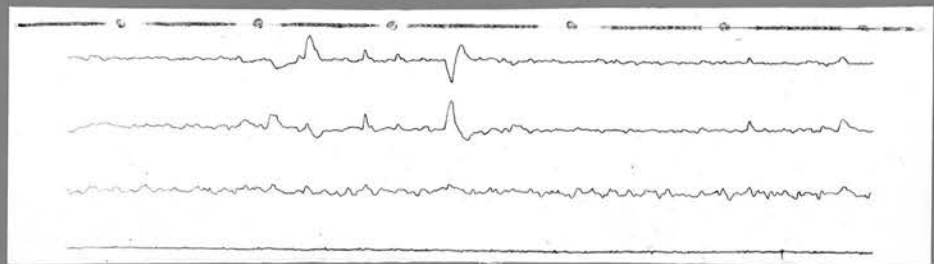
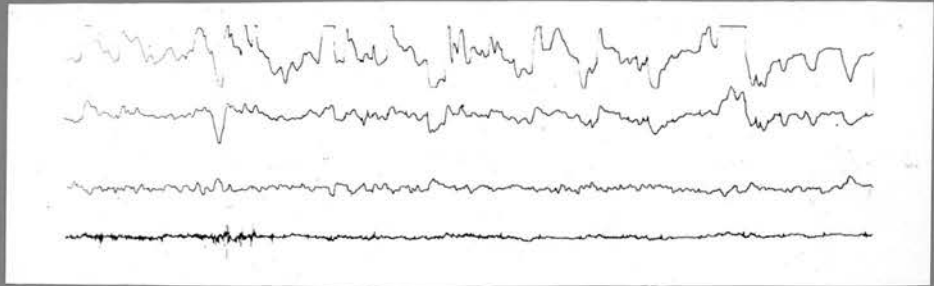


Fig. 112

Variation in intensity of rapid eye movements.

Upper traces show continuous high amplitude eye movement potentials on the 10th night after the overdose.

Lower traces show short bursts of low amplitude eye movement potentials 35 nights after the overdose.

responding to painful stimuli. She regained consciousness on the second day and was transferred to North Wing of the Royal Edinburgh Hospital for psychiatric in-patient care.

Her sleep was first recorded on the third night. Drug-induced EEG fast activity disappeared on the 11th night. Her early night intra-sleep restlessness is indicated by Fig. 113. It increased to a peak on the 8th night and declined in the subsequent month. The percentage of sleep spent as REM sleep rose from nil on the third night to a peak of 42.4% on the eighth night, with eventual stabilisation around 18% after a further three weeks (Fig. 114).

She had no stages 3 + 4 sleep on the third night, 11% the next night and this percentage rose irregularly to values over 30% by the third week. Her total sleep duration on night 3 was 517 minutes and this duration fell steadily on successive nights till the twelfth night, when she slept only 203 minutes and then rose to a more normal figure in the subsequent week (Fig. 115). She received no drugs or other treatment during the period of study.

Clinical examination suggested mild organic brain impairment and this was confirmed by psychological testing on which, 24 days after overdose, she showed specific impairment in the ability to learn new material and greater impairment in retention, particularly of visual items, though general intelligence (Wechsler Full Scale, I, Q = 120) was not reduced. It was assumed that it was owing to meningitis and not overdose.

PATIENT 6/

SLEEP AFTER NITRAZEPAM OVERDOSE.
PATIENT 5

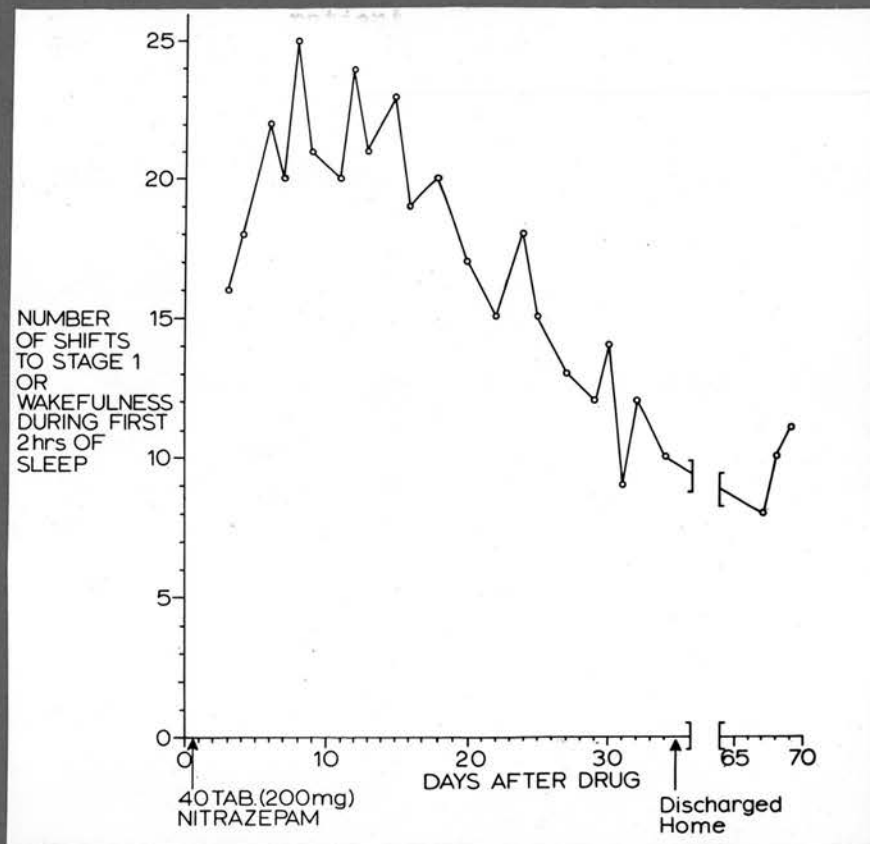


Figure: 113

Intra-sleep restlessness in the early night rises to high levels from the eighth to fifteenth nights and declines gradually in the succeeding three weeks. Nitrazepam-induced EEG fast activity disappeared on the eleventh night in this patient.

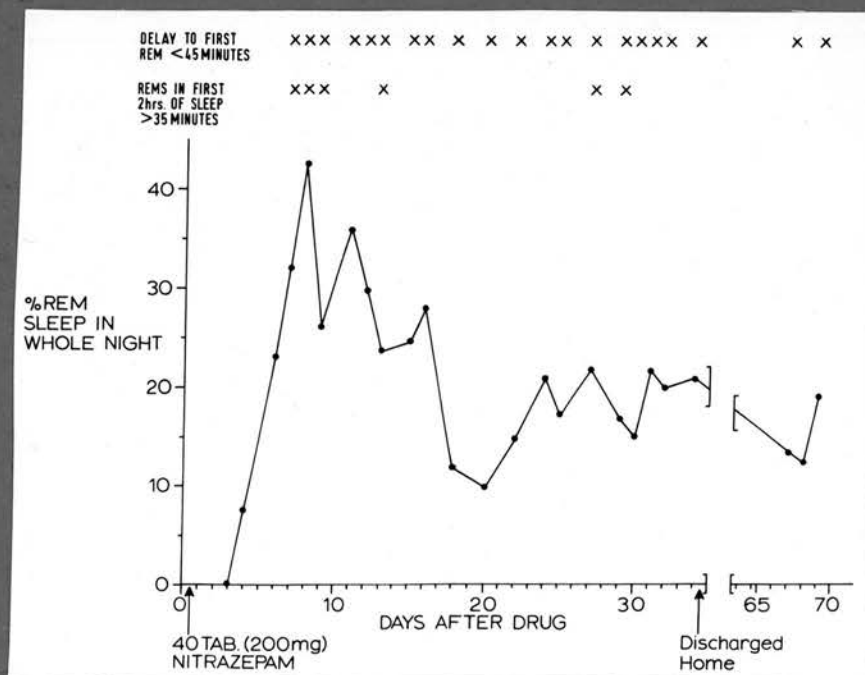


Figure: 114

REM sleep was suppressed after the nitrazepam overdose, rose to the very high level of 42.2% on the eighth night, appeared to fall below her normal after three weeks and thereafter rose slightly to a low-normal figure.

SLEEP AFTER NITRAZEPAM OVERDOSE.

PATIENT 5

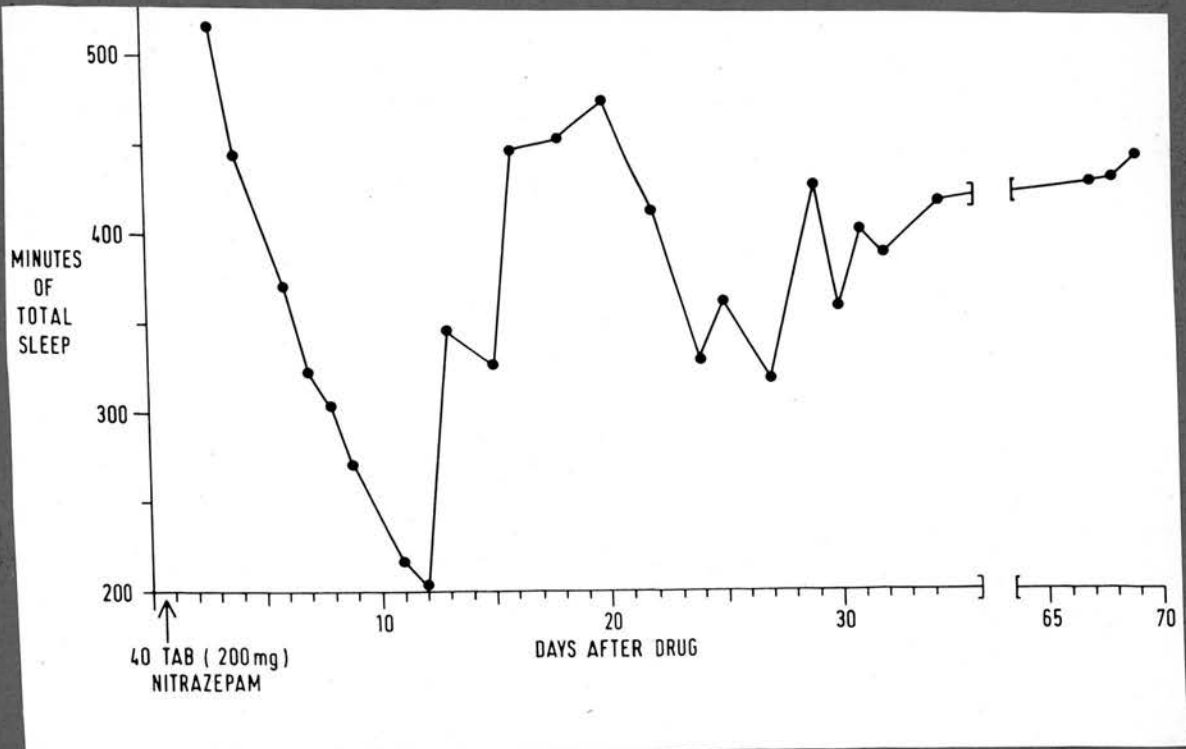


Figure:- 115

Total nocturnal sleep duration was very high at first, declined steadily to under three and a half hours on the twelfth night (just after EEG fast activity indicated the drug had left the brain) and recovered to 6-7 hours by the end of the study.

PATIENT 6: (11/103/CQ)

A 28 year old female who had not been taking any drugs took 80 tablets (8000 mg.) of phenobarbitone and was admitted to the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh on the 8th March, 1969. On admission she was drowsy but after the stomach washout she was deeply comatose and totally unresponsive to all stimuli. Continuous EEG monitoring was started soon after admission. Her initial EEG record revealed Grade IV changes. The clinical course of her illness and EEG changes seen during acute phenobarbitone poisoning are described in detail in Project 2. (see case histories - No. 1).

She regained consciousness after 96 hours of coma and was transferred to the Royal Edinburgh Hospital for psychiatric in-patient care where further studies were continued.

After one week she was ambulant, and, to the clinical observer, fully conscious. Her blood phenobarbitone level (Fig. 116) at the time of admission to the Poisoning Treatment Centre was 9.2 mg.%. It was 9.7 mg.% after 96 hours at the time when she became conscious. The level had fallen to 0.8 mg.% on the 19th day after drug ingestion, on which day she asked for her discharge.

Her all-night sleep was recorded from the 6th post-overdose night onwards. Her sleep was disturbed as indicated by increased intra-sleep restlessness (Fig. 117). The number of shifts to stage 1 and wakefulness in the first two hours of sleep rose gradually from 16 on the 6th night to 37 on the 18th night. At the same time her blood phenobarbitone level fell steadily from 7.9 mg.% on 6th post-overdose night to 0.8 mg.% on the 18th night.

Total/

PHENOBARBITONE OVERDOSE.
PATIENT 6

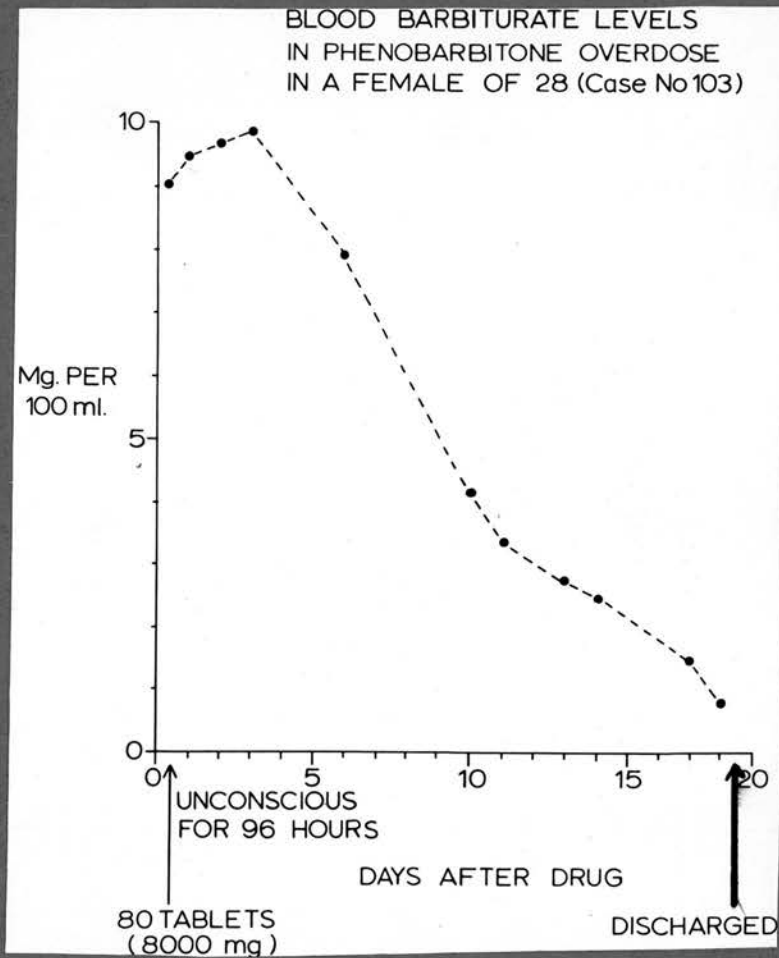


Figure: 116

Blood phenobarbitone estimation actually revealed a higher level when, after 96 hours, she regained consciousness than had been present on admission. Note that after 10 days with a fully ambulant patient very high blood levels persist and that three weeks would apparently have been needed to clear the drug from the blood.

Total nightly sleep duration, which was 509 minutes on the first recorded night, also declined gradually and was 387 minutes on the night before discharge. The sleep EEGs showed an excess of drug-induced fast activity which was present till the sixteenth night. Combined stages 3 and 4 of NREM sleep increased irregularly during the time of study and were 15.9, 10.8, 18.8, 19.0 and 23.9% on nights 6, 10, 15, 16 and 18 respectively.

REM sleep duration in the whole night (Fig. 118) was reduced (7.7%) and contained only few, small eye movements on the 6th post-overdose night but there was gradual accentuation and the whole-night percentage of REM sleep rose to 36.5% on the 18th night. Other abnormalities like early onset of the first REM period in the night and increased amount of REM sleep occurring within the 1st 2 hours of sleep were also seen as whole-night REM sleep percentage increased and were present on the 18th post-overdose night, the day before her discharge.

PATIENT 7:- (20/114/EW)

A 21 year old female, who was not regularly taking hypnotics was admitted to the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh on 8th June, 1969, after having taken about 15 tablets (3000 mg.) of sodium amylobarbitone.

On admission she was only drowsy and could be aroused to verbal responses. Her blood pressure was 110/65 mm.Hg. and pulse 76 per minute, regular and good volume. Physical examination was normal in all respects. Stomach washout was productive and she was/

SLEEP AFTER PHENOBARBITURATES OVERDOSE.

PATIENT 6

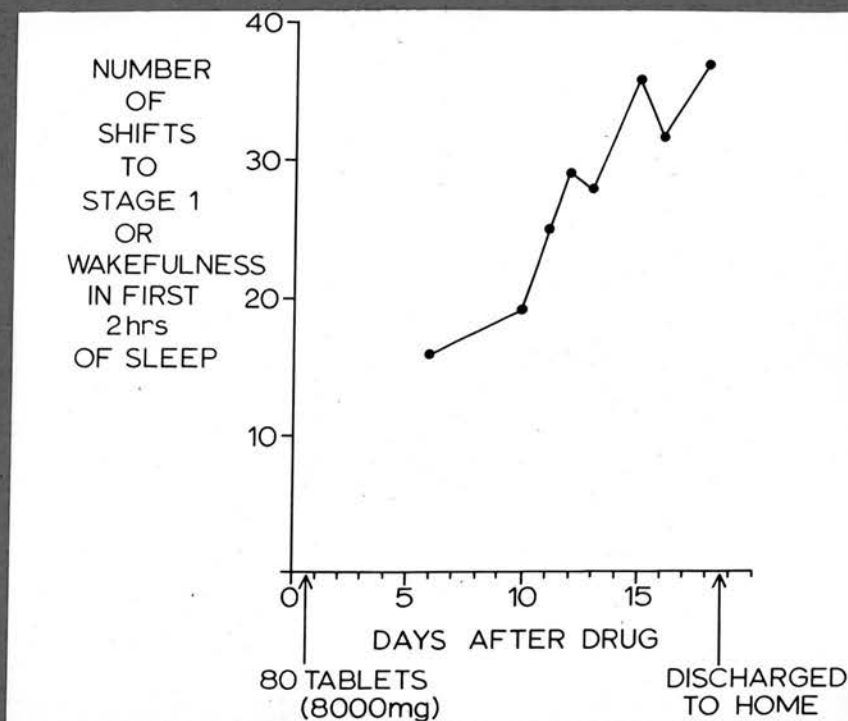


Figure:- 117

When compared with Fig 116 it may be seen that as the blood level of phenobarbitone fell, so the intra-sleep restlessness increased and would presumably have reached a maximum around three weeks post-overdose.

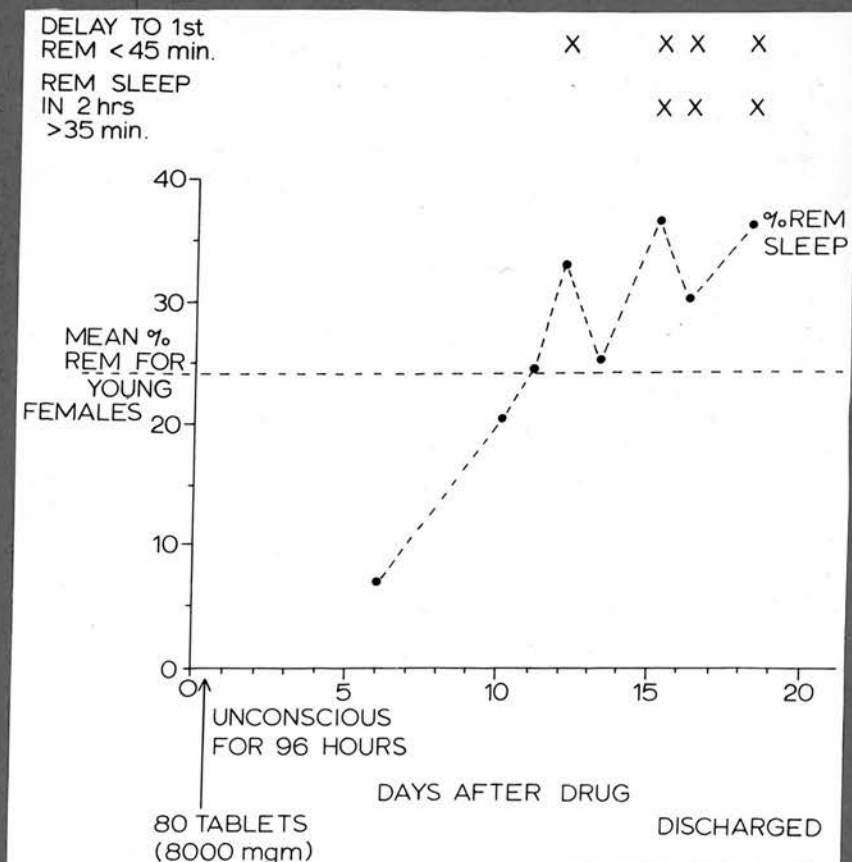


Figure:- 118

REM sleep was suppressed by the drug but a rebound occurs and it appears that the curve would have had a maximum at around three weeks post-overdose.

was fully conscious 24 hours after admission. She was seen by the consultant psychiatrist and transferred to the North Wing of the Royal Edinburgh Hospital for psychiatric in-patient care where further studies were carried out.

Her sleep was recorded on the fourth night and the early night intra-sleep restlessness increased to a peak of 20 shifts in the first two hours of sleep on the 6th night and then fell to 4 shifts by discharge on the 17th day. Likewise her all-night percentage of REM sleep (Fig. 119) rose to a peak of 30.4% on the 6th night and quickly fell away on later nights.

Four days after drug ingestion her blood barbiturate level was less than 0.5 mg.% and it was zero the following day. EEG barbiturate-induced fast activity was visible only on the fourth night. The combined stages 3 + 4 of NREM sleep gradually rose from 27% on the 4th night to 42.2% on the 16th night after drug ingestion.

PATIENT 8 (40/78/BH)

A 29 year old man was admitted to the Poisoning Treatment Centre, Royal Infirmary, Edinburgh on 21st February, 1969, after being found unconscious that evening. It was discovered later that he had taken 25-30 tablets (2500-3000 mg.) of sodium butobarbitone.

On admission he was deeply unconscious. Blood pressure 105/65 mm.Hg; pulse 76, regular, fundi normal. His pupils were somewhat constricted, reacting to light; cough and gag reflexes present. Knee and ankle jerks symmetrically increased/

REM SLEEP AFTER SODIUM AMYLOBARBITONE OVERDOSE.

PATIENT 7

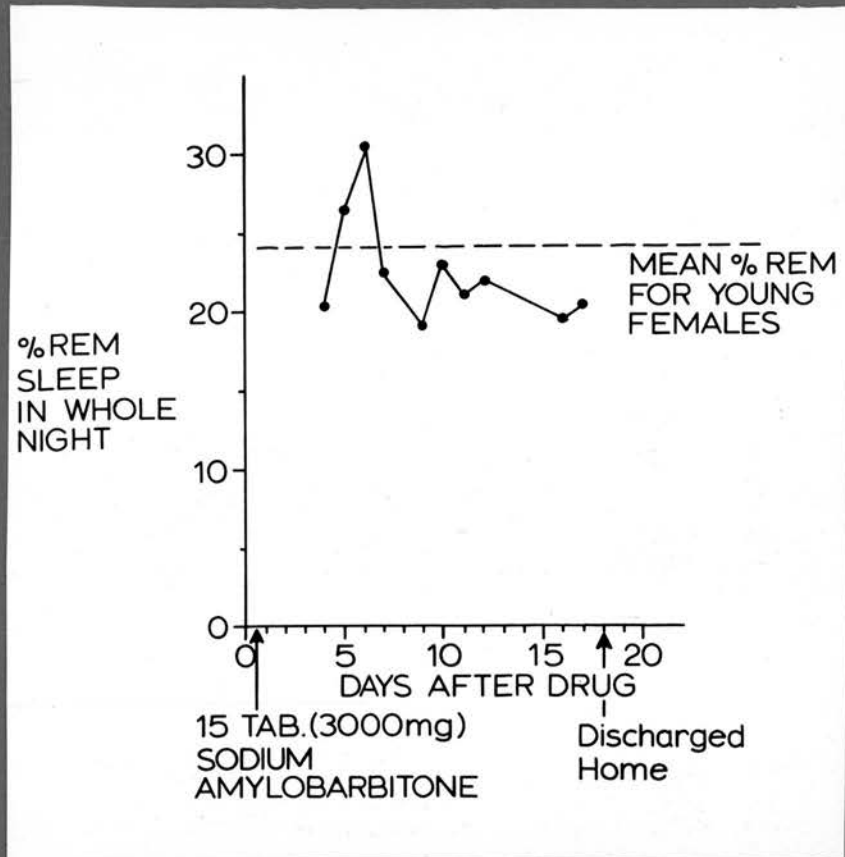


Figure:- 119

Effect of a small overdose of sodium amylobarbitone in a woman not previously receiving them. There appears to be a small and brief REM sleep rebound with a peak of 30.4% on the sixth night with a quick fall to her presumed normal of around 20% in the whole night. No definite early-night paradoxical (REM) sleep abnormalities occurred. Her intra-sleep restlessness was also maximal on the sixth night.

increased with reduction in biceps and triceps jerks and flexor plantar responses.

Gastric aspiration and lavage were performed with no return of indentifiable tablet material. Continuous EEG monitoring was started two hours after his admission to the ward and the initial EEG record revealed Grade IV EEG changes. His rectal temperature was 35.5°C and serum barbiturate level 3.0 mg.%. He gradually improved and regained consciousness after 36 hours of coma and later on he was very obstreperous and violent for a short time. He was seen by the consultant psychiatrist on 25th February and transferred to the Royal Edinburgh Hospital for psychiatric in-patient care.

His all-night sleep was recorded on the 4th post-overdose night. He slept for 182 minutes and no EEG barbiturate fast activity was seen. REM sleep began abnormally early, namely only 13 minutes from sleep onset, and occupied an excess of the first two hours of sleep, namely 52 minutes with a whole night sleep percentage of 29%. His aggressive behaviour did not permit further study.

PATIENT 9: (36/108/MM)

A 41 year old housewife, after an argument with her husband for the fifth time took an overdose of drugs. On this occasion it was of 30 tablets (3000 mg.) of sodium pentobarbitone. She was admitted to the Poisoning Treatment Centre deeply unconscious and on the 3rd day, after recovery of consciousness, transferred to psychiatric care.

Her/

Her sleep was recorded on the 3rd, 4th and 6th nights during which there were successive increases in intra-sleep restlessness (19, 22 and 24 shifts in the first 2 hours) in stages 3 + 4 sleep (6.9, 9.2, and 15.6%) and in REM sleep (Fig.120) from 19.3% to 37.8% in the whole night with early onset of REM sleep and early night excess. EEG barbiturate fast activity disappeared on the sixth night on which night she had barely four and a half hours total sleep. She took her own discharge on the seventh day.

PATIENT 10.(PB).

A 20-year old nurse, who had taken an overdose of ferrous sulphate a year earlier, took 150 tablets, or 50 grams of aspirin. Two hours later she was admitted to the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh on 3rd June, 1969. On admission she was conscious. Gastric aspiration and lavage was performed and some tablets were obtained in the return. In view of her high blood salicylate level (70 mg. percent) forced alkaline diuresis was commenced, after which her salicylate level dropped to 40 mg.%. After clinical recovery from acute drug poisoning she was transferred to psychiatric care.

Sleep was recorded on the fourth post-overdose night. Intra-sleep restlessness was low, rising from 7 shifts in the first two hours on the fourth night to 10 on the sixth and falling to 6 on the ninth and tenth nights. REM sleep showed some signs of possible rebound increase with early onset, after 42 and 39 minutes on the sixth and seventh nights but as Fig.121 shows/

REM SLEEP AFTER PENTOBARBITONE OVERDOSE
Patient 9 - Female, 41 years old.

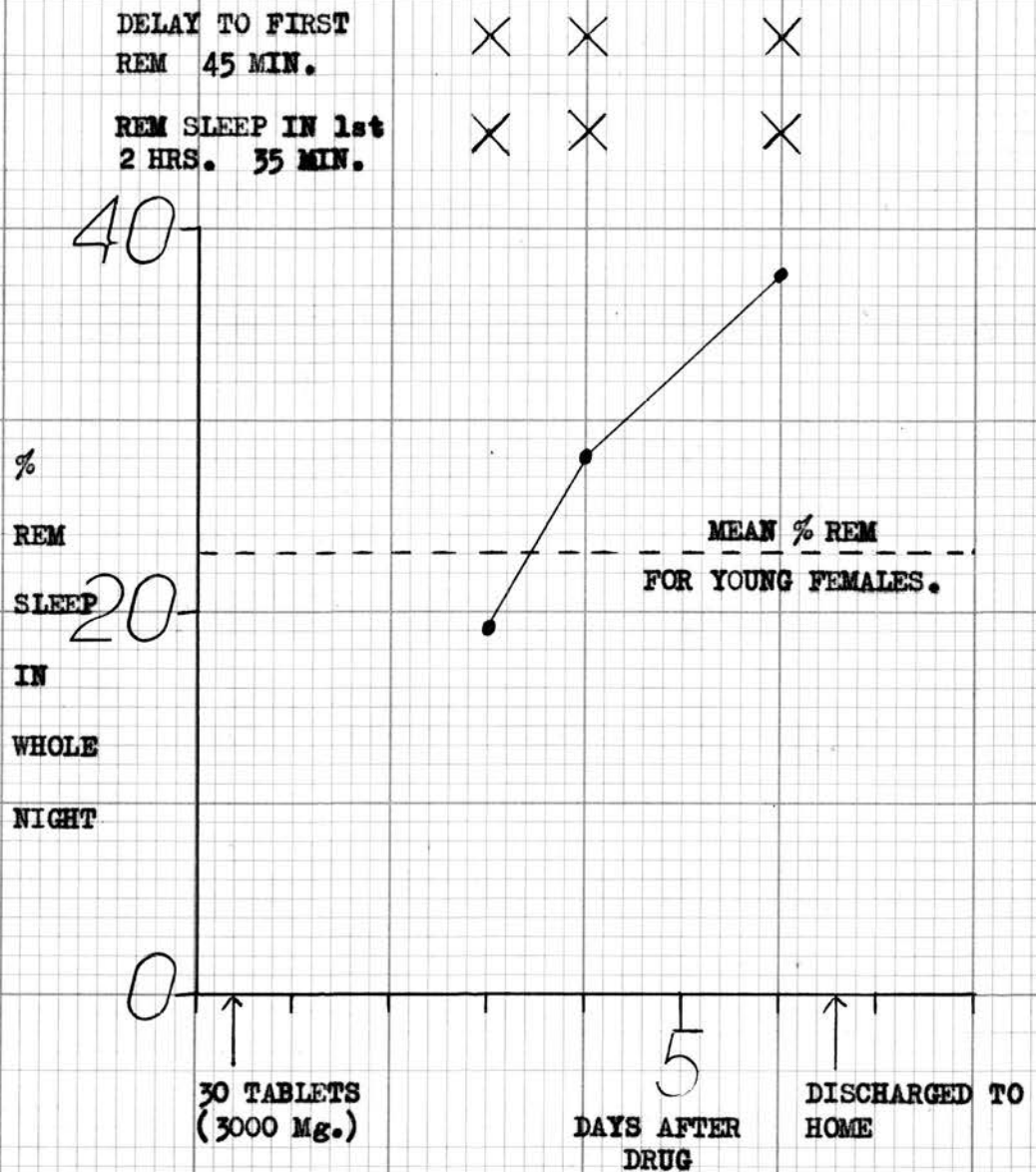


Figure 120:

The shape of the curve suggests that REM sleep was suppressed by the drug but that a rebound occurred, with 37.8% on the 6th night. The excess of REM sleep and its early onset, indicated by the stars across the top of the figure, were observed on the 6th night, the night before she took her discharge.

REM SLEEP AFTER SALICYLATE OVERDOSE.

PATIENT 10.

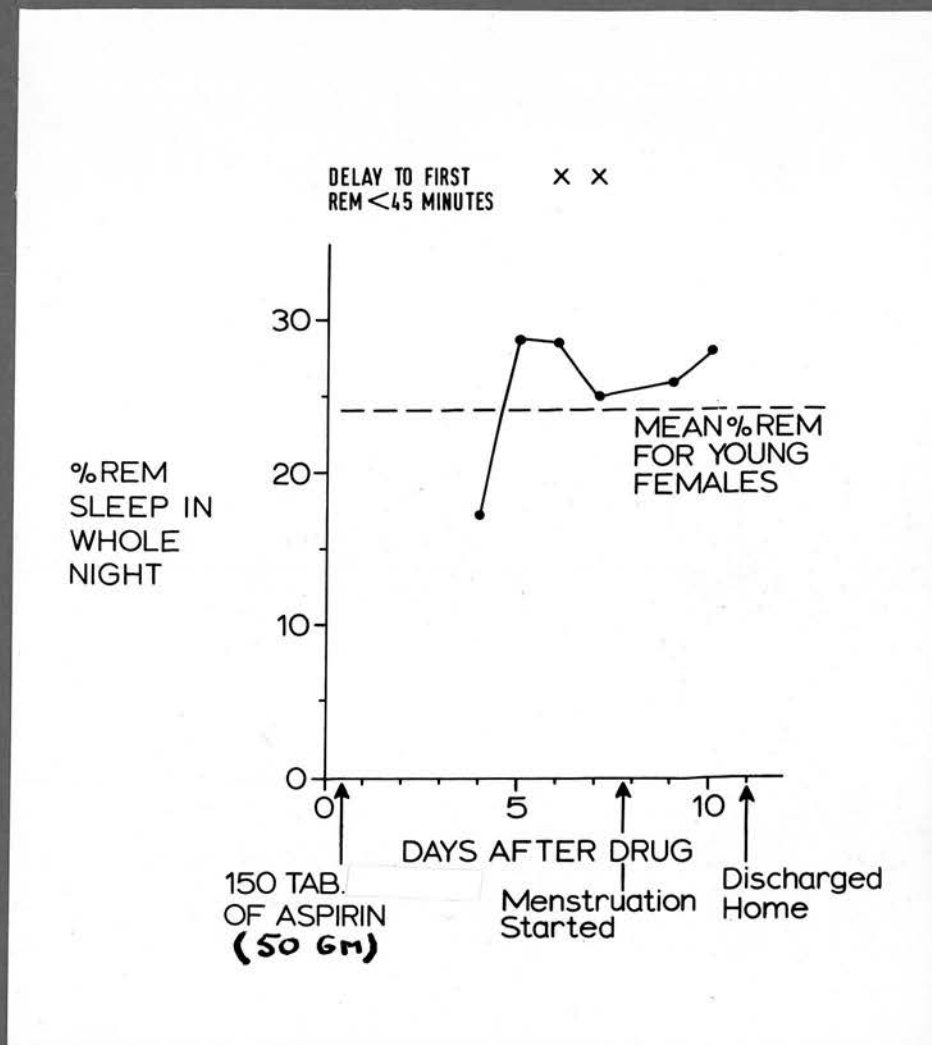


Figure: 121

In contrast to the hypnotics, acetyl salicylic acid, in massive overdose, has only slight effects possibly suppressing REM or paradoxical sleep at first with minimal signs of rebound on the sixth and seventh nights. The immediate pre-menstrual period can be associated with a small increase in REM sleep, and, in view of the smallness of the effects noted, the time of menstruation onset is consequently indicated.

shows, there was little remarkable. Stages 3 + 4 sleep showed no trends or features of note and totalled 20-30% each night. Blood salicylate had fallen below 5 mg.% by the sixth day.

PATIENT 11 (119/123) CM)

A sixteen year old girl took 40 tablets (800 mg.) of fenfluramine and was admitted to the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh on 15th July, 1969 at 02.30 hours. Continuous EEG monitoring was started three hours after admission to the ward. Her EEG record revealed Grade I EEG changes. The clinical course in the hospital described under Project No. 2. (See case histories - No.18).

She did not appear to sleep on the first night. Her whole-night sleep was recorded by electroencephalography on nights 3, 4, 5, 6, 8, 9, 11, 12, 14, 15 and 19 after overdose. It was frankly abnormal on night 3, when 11 minutes of REM sleep occurred at initial sleep onset, instead of after about an hour as is normally the case (Oswald, 1968). Her all-night percentage of REM sleep was also highest on that night. There appeared to be accentuation of EEG sleep spindles on the same night. The percentages of sleep as REM sleep (Fig. 122) on the various nights were 29.8, 24.1, 22.8, 27.1, 22.9, 20.2, 24.2, 25.8, 26.7, 23.1 and 20.8 respectively - all within normal limits. There were two other features which also suggested abnormality of rebound type, namely, a short delay of 45 minutes (night 4) from sleep onset to first REM sleep and excess REM sleep within the first two hours of sleep, namely, 31 minutes (Night 5).

PATIENT 12/

REM SLEEP AFTER FENFLURAMINE OVERDOSE.
IN TWO FEMALE PATIENTS.

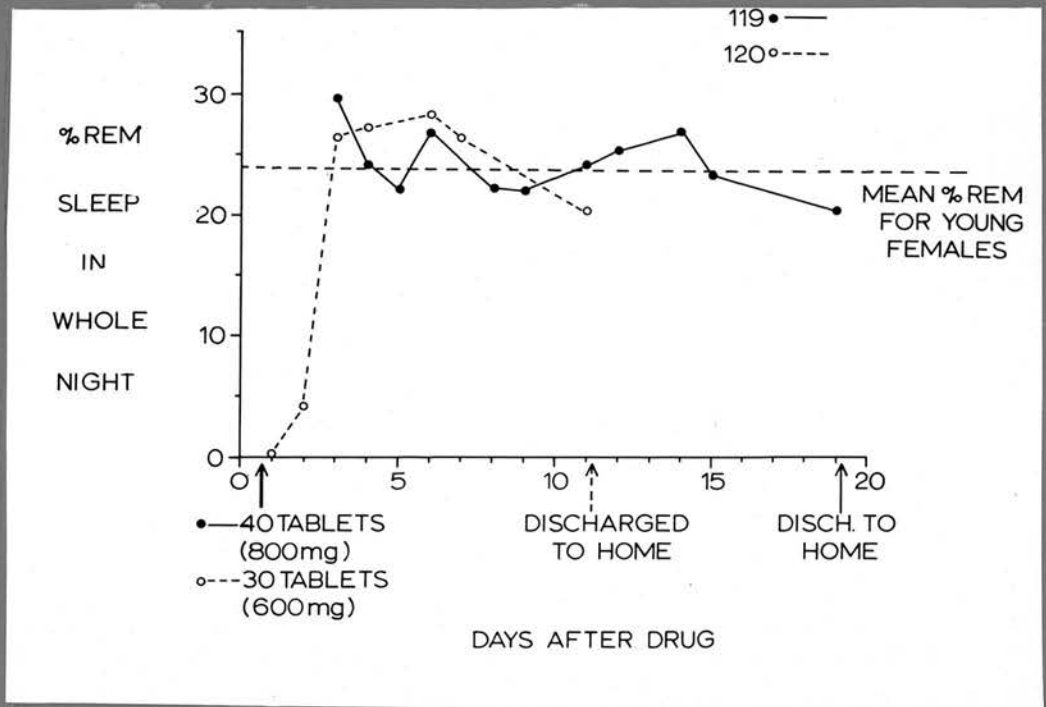


Figure:122

Fenfluramine, in massive overdose, has only slight effects, possibly suppressing REM sleep at first (Patient 120) with minimal signs of rebound on the second (patient 119) and sixth (patient 120) nights. In patient 119 an early onset of REM sleep (night 4) and excess REM sleep within the 1st two hours of sleep (night 5) was also noted. The first two values on the graph for patient 120 are inspired guesses based upon the 95 minute and 340 minute of sleep recorded on these nights.

PATIENT 12. (120/124/M)

A 16 year old girl was admitted to the Regional Poisoning Treatment Centre, Edinburgh at 22.00 hours on the 23rd July, 1969 after having taken 30 tablets (600 mg.) of fenfluramine two and a half hours prior to admission. On admission she was conscious. Continuous EEG monitoring was started soon after admission to the ward. The clinical course of her illness is described in Project No. 2 (see case histories - No. 19).

She fell asleep at 02.30 hours, four and a half hours after admission, and her EEG was continuously recorded for the first 95 minutes of sleep. The record was abnormal in that continuous muscle artefact was present in all channels, superimposed on the EEG sleep traces. In addition Stages 3 and 4 EEG sleep appearances, which would normally be seen in the first hour of sleep, were not present, the record consisting only of stage 2 sleep with brief periods of stage 1. No REM sleep was seen.

On her second night the first 5 hours. 40 minutes of sleep was recorded. Stage 3 was present early in the night. The excess of continuous muscle artefact was still detectable but much reduced. REM sleep did not appear till after 4 hours 20 minutes and lasted only two minutes. There appeared to be some enhancement of the EEG sleep spindle activity.

Her sleep was also recorded for the whole night on nights 3, 4, 6, 7 and 11. The REM sleep (Fig. 122) percentages were all normal, namely, 26.8, 27.6, 28.0, 26.3, 20.8 respectively. REM sleep began early, after 46 minutes on night 4 and occupied 31 minutes in the first two hours of sleep on night 6.

DISCUSSION

A syndrome which may include restlessness, insomnia, delirium and convulsions occurs after withdrawal of almost all hypnotics, if they have been taken in sufficient dose and for long enough (Wulff, 1959; Hudson and Walker, 1962; James, 1963; Fraser et al., 1954). Recent work has shown that REM sleep is grossly increased in the delirium of alcohol and barbiturate withdrawal (Gross et al., 1966; Greenberg and Pearlman, 1967; Evans and Lewis, 1968; Lewis, 1969). Therefore it seems likely that all hypnotics have these effects on human sleep in some measure.

In this study restlessness, insomnia, delirium and also EEG epileptic-type abnormalities were observed in patients in whom a high degree of tolerance and dependance had presumably been acquired in the presence of massive concentrations of drug. Patient 6 (phenobarbitone case) had taken no previous drugs but after four days had acquired such tolerances to continuing high concentrations of phenobarbitone that she regained consciousness.

The phenomena described cannot be deemed non-specific responses to hospital admission. Restlessness at night, for example was not maximal in these patients at initial study but maximal about the time the drug ceased to act. Patient 6 got more and more restless, slept less and less, and got more and more REM sleep as the three weeks to full excretion of phenobarbitone/

proceeded. Patients 4 and 5 (nitrazepam overdose) also well illustrate the same phenomena, which in their cases, reached a peak at about the tenth post-overdose day.

The relation between the duration of drug action and the observed phenomena also means that they could not be interpreted as sequelae to the emotional crisis that led to the taking of an overdose. In addition aspirin overdose (Patient 7) serves as a control. Aspirin is a drug which stimulates respiration but has only slight effects on mechanisms of consciousness and it had only slight effects on the variables measured. Overdose of fenfluramine in two young women (Patients 11 and 12) had equally slight effects (Riley et al., 1969), adding further evidence that neither the original psychological state nor the fact of hospital admission could be held responsible. I believe the important variables are the nature of the drug, the duration of exposure to it and the dosage. It should be added that many of the post-overdose effects are seen not only after hypnotics but after overdose of such drugs as imipramine (Lewis and Oswald, 1969), debrisoquine (Oswald, I. and Dunleavy, D., unpublished), phenelzine (Akindole et al., 1970) and, by inference, amphetamine (Oswald and Thacore, 1963). Similar phenomena have been observed too in the weeks after experimental administration of drugs to normal volunteers, for example, nitrazepam and sodium amylobarbitone (Oswald and Priest, 1965) and heroin (Lewis et al., 1970). These volunteers had neither been driven to take overdoses nor admitted for treatment.

Certain lessons may be drawn. When psychiatric assessment is made in the day or two after recovery of consciousness a patient may still be very much under the influence of an/

anxiety-reducing drug. If it is decided that the patient should go straight home, as do 80% at Edinburgh, it may be several days later that withdrawal insomnia, nightmares (often an accompaniment of raised REM sleep), confusion, or even delirium, become manifest. A desire to resume hypnotics, contrary to medical wishes, can be understood.

Regular intake of hypnotic drugs can result, after their withdrawal, in restlessness, insomnia, nightmares and abnormally increased REM sleep for several weeks (Oswald and Priest, 1965). The phenomena were extreme in the present study and prior-to-overdose medication cannot be held solely responsible for e.g. Patient 6. In the study of Oswald and Priest (1965), as in this study, a close relation between delay to drug-elimination (indicated by persisting EEG fast activity) and the delay to peak REM sleep rebound after drug withdrawal was present. This delay seems to be a general guide to persisting drug action on the brain (Oswald, 1969) and a better one than blood levels, which can be no guide after tricyclic drug overdose (Lewis and Oswald, 1969).

The safety of nitrazepam, Matthew et al., (1969) means it is to be preferred to its contemporary rivals, but it is not rapidly eliminated to judge by EEG fast activity (Oswald and Priest, 1965), and one must not expect normal motor co-ordination, a customary degree of emotional stability or good judgement, just because a patient has remained conscious after overdose of nitrazepam. The slowness of phenobarbitone elimination revealed in/

this study serves once more to underline the unsuitability of phenobarbitone as a hypnotic.

An impressive feature of the results is the length of time, of up to two months, seen in the various recovery-period curves. It has been argued that such slow recoveries of brain function are dependent upon the slowness of neuronal protein synthesis (Oswald, 1969). After severe overdose the patient may be unconscious two days, ill for a few more, and appear superficially normal after a week. One is reminded of a kick on the shins, where temporary incapacity may be followed by only a day or two of limping, yet the bruise takes a couple of months to disappear. In the brain, repair after chemical injury can likewise take many weeks.

Evidence accumulates that while sleep may be a general restorative, the phase known as REM sleep, with its very high brain blood flow, may be specifically concerned with brain repair, whereas stages 3 and 4 (EEG slow wave) sleep are especially concerned with general bodily repair (Oswald, 1969). It is noteworthy that, in patient 1, Stage 4 sleep took a month after overdose to re-appear. On the other hand, at a time when stages 3 and 4 sleep were absent, REM sleep seemed to have high priority and was increased above normal. This could hardly be a non-specific result of sleep interruption since the latter alone will decrease REM sleep. The observations thus support the belief that REM sleep has a restorative function for the brain.

VI. APPENDIX

SLEEP AFTER MANDRAX OVERDOSE

(PATIENT NO. 1)

Number of Nights	1	2	3	4	5	6	7	8	9	10	11	13	14	16	17
Date	20/3	21/3	22/3	23/3	24/3	25/3	26/3	27/3	28/3	29/3	30/3	31/3	2/4	3/4	6/4
Delay to Sleep in Minutes	-----UNCONSCIOUS -----														
Delay to First REM Period in Mins					0	0	0	0	0	0	0	6	12	8	41
REMS in Mins. During first two hrs. of sleep					11	55	98	88	68	30	30	30	54	57	50
WAKEFULNESS during Night in Mins.					382	275	318	265	230	381	118	185	69	1155	937
% Stage 1					27.2	20.7	13.8	15.8	29.3	4.6	6.2	15.9	14.8	10.1	6.7
% Stage 2					-	-	-	3.9	27.4	59.4	59.0	39.8	29.8	35.8	44.1
% Stage 3					-	-	-	-	-	-	-	-	-	2.0	5.0
% Stage 4					-	-	-	-	-	-	-	-	-	-	-
% REM Stage					72.8	79.3	86.2	77.5	42.3	36.9	34.8	45.3	55.4	51.1	44.2
Shifts to W Or Stage 1 in first two hrs. of sleep					34	38	39	37	34	36	31	29	33	26	27
Total Sleep time in Mins.					12	69	139	125	207	89	307	246	388	387	403

SLEEP AFTER MANDRAX OVERDOSE

(PATIENT NO.1)

Number of Nights	18	19	20	21	22	23	25	26	27	29	30	31	33	34	35	36	37
Date	7/4	8/4	9/4	10/4	11/4	12/4	14/4	15/4	16/4	18/4	19/4	20/4	22/4	23/4	24/4	25/4	26/4
Delay to sleep in Minutes	13	11	12	9	12	8	16	14	16	8	26	11	17	17	53	14	27
Delay to First REM Period in Mins.	72	35	22	15	17	60	75	77	37	49	84	58	53	45	70	57	17
REMS in Mins. during first two hrs. of sleep	33	38	44	47	19	10	59	23	57	44	54	12	21	39	41	12	37
WAKEFULNESS during Night in Mins.	52	118	51	58	93	31	86	73	20	77	100	42	47	37	91	47	65
% Stage 1	9.7	19.4	8.0	15.5	9.0	5.3	12.8	12.6	11.7	5.2	8.7	7.7	9.3	10.5	8.3	9.4	7.8
% Stage 2	53.6	52.4	52.3	36.2	60.5	41.4	42.8	44.3	45.6	49.9	46.2	57.8	54.3	49.4	57.2	50.1	57.6
% Stage 3	-	-	-	7.1	10.0	10.6	10.7	14.0	8.0	11.2	10.6	14.2	15.1	14.0	11.7	17.2	15.8
% Stage 4	-	-	-	-	-	-	-	-	-	-	-	3.7	3.4	4.1	4.1	9.3	-
% REM Stage	27.7	27.2	39.7	41.2	20.5	40.0	34.0	29.1	34.7	33.7	36.5	16.6	17.7	25.6	18.8	22.0	18.8
Shifts to W or Stage 1 in first two hrs. of sleep	23	21	22	24	23	19	15	14	16	19	15	12	14	13	15	11	12
Total sleep time in Mins.	395	383	413	453	391	402	399	422	412	396	334	378	413	418	406	426	403

SLEEP AFTER METHYRNYLON OVERDOSE

(PATIENT NO. 3)

Number of Nights	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Date	1/3	2/3	3/3	4/3	5/3	6/3	7/3	8/3	9/3	10/3	11/3	12/3	13/3	14/3	15/3	16/3	17/3	18/3	19/3	20/3	21/3	22/3	23/3	24/3	25/3
Delay to sleep in Minutes					48	84	76	61	66	94	-	39	-	91	32	81	101	92	75	45					
Delay to First REM Period in Mins.					75	46	61	79	61	91	-	40	-	52	71	58	50	66	81	82					
REMS in Mins. during first two hrs. of sleep					34	32	53	27	49	29	-	35	-	14	13	14	27	11	29	28					
WAKEFULNESS during Night in Mins.					0	2	4	2	2	18	-	11	-	6	29	23	11	7	1	3					
% Stage 1					10.4	6.4	9.8	11.8	10.1	12.5	-	7.8	-	7.4	4.7	9.1	8.6	8.4	5.8	6.					
% Stage 2					57.7	48.9	40.0	46.7	46.3	41.2	-	48.4	-	42.6	40.2	44.2	40.8	48.3	48.4	49.					
% Stage 3					2.3	6.3	3.9	5.5	5.8	6.1	-	3.7	-	5.7	7.1	8.2	9.5	8.2	8.4	5.					
% Stage 4					3.1	1.4	4.0	4.0	4.1	5.7	-	6.1	-	6.3	3.5	6.0	5.1	8.1	6.9	8.					
% REM Stage					26.5	37.0	42.3	32.0	33.7	34.5	-	34.0	-	38.0	44.5	32.5	36.0	27.0	30.5	29.					
Shifts to W and Stage 1 in first 2 hrs. of sleep					26	29	27	24	32	28	-	26	-	27	27	25	23	22	24	17					
Total sleep time in Mins.					316	378	384	448	435	427	-	470	-	415	399	397	394	422	418	419					

UNCONSCIOUS

CONSCIOUS - SLEEP RECORDED - TOTAL INSOMNIA

SLEEP RECORDED - NO SLEEP AT ALL

Unco-operative (Paranoid, hallucinated)

RECORDING NOT POSSIBLE ONLY OBSERVED - INSOMNIA

SLEEP AFTER METHYRYLON OVERDOSE

(PATENT NO. 3)

Number of Nights	25	26	28	30	31	33	34	36	38	39	40	42	43	45	47	48	49	50	52	53	55
Date	26/3	28/3	30/3	31/3	2/4	3/4	5/7	7/4	8/4	8/4	9/4	11/4	12/4	14/4	16/4	17/4	18/4	19/4	21/4	22/4	24/4
Delay to sleep in Minutes	40	20	34	59	37	49	40	26	35	92	53	33	33	28	49	22	52	43	34	49	40
Delay to First REM Period in Mins.	30	79	74	71	79	57	50	67	59	54	59	62	57	79	86	51	61	44	47	50	50
REMS in Mins, during first two hrs. of sleep	19	25	39	17	31	29	46	21	10	44	29	20	21	26	23	17	31	20	40	8	8
WAKEFULNESS during Night in Mins.	8	6	1	5	26	3	4	1	1	-	3	2	2	2	13	12	2	-	6	1	5
% Stage 1	9.3	8.9	4.8	11.5	11.9	6.0	6.1	9.1	6.0	6.1	5.6	8.5	8.3	6.1	7.4	4.6	5.8	3.1	4.3	5.0	5.0
% Stage 2	48.4	48.9	49.3	43.4	35.6	45.0	39.4	43.0	46.0	40.4	43.5	42.6	48.1	50.3	50.4	51.3	47.2	50.7	48.2	49.8	49.8
% Stage 3	8.8	8.0	10.3	8.6	9.1	9.0	8.1	9.3	5.9	8.8	11.2	8.1	5.4	8.0	9.8	8.8	6.2	2.5	7.1	7.8	7.8
% Stage 4	7.8	10.5	10.5	9.5	10.7	10.3	10.7	11.1	13.0	11.2	13.4	13.8	9.2	8.8	10.9	11.1	12.1	12.2	10.6	12.1	12.1
% REM Stage	25.7	23.7	24.6	27.0	32.9	30.5	35.7	27.5	28.1	33.5	28.3	27.0	29.0	26.8	21.5	24.2	28.7	30.9	29.8	24.7	24.7
Shifts to W and Stage 1 in first two hrs. of sleep	13	20	11	10	11	13	15	14	12	13	11	7	10	13	9	12	8	11	11	11	11
Total sleep time in Mins.	371	367	485	460	378	414	469	462	432	460	417	468	437	447	481	425	457	489	485	423	423

SLEEP AFTER NITRAZEPAM OVERDOSE

(PATIENT NO. 4)

Number of Nights	1	2	3	4	5	6	7	8	9	10	11	13	14	16	17	18
Date	26/2	27/2	28/2	1/3	2/3	3/3	4/3	5/3	6/3	7/3	8/3	10/3	11/3	13/3	14/3	15/3
Delay to Sleep Onset in Mins.	8	75	41	31	45	84	185	14	93	194	61	62	53	183	157	20
Delay to first rapid eye Movement (REM) period in Mins.	256	650	120	63	74	62	59	72	67	58	45	26	40	52	16	37
REMS in first two hrs. of sleep in Mins.	-	10	-	4	12	17	15	14	36	49	22	60	22	20	33	16
WAKEFULNESS in Mins.	-	-	-	120	76	-	-	7	110	-	15	102	1	7	22	106
% Stage 1	0.9	0.6	1.6	4.6	1.8	2.4	2.6	5.3	10.7	3.8	3.5	4.7	1.9	2.1	2.4	3.7
% Stage 2	84.7	73.0	87.6	57.2	69.3	54.6	40.8	43.7	32.0	32.6	47.0	29.2	33.6	29.8	30.3	30.2
% Stage 3	2.4	16.4	-	7.1	2.2	5.9	11.0	2.3	8.3	3.4	4.5	11.8	7.7	6.9	9.6	11.8
% Stage 4	6.7	-	-	19.0	10.3	10.0	12.2	17.0	22.7	14.0	9.3	15.7	14.2	18.9	18.9	15.1
% REM Stage	6.3	11.0	10.3	12.1	16.4	16.4	27.1	33.4	23.7	44.8	35.6	36.6	42.7	42.3	38.6	30.2
Shift to W or Stage 1 in first two hrs. of sleep	14	15	13	16	17	18	16	14	15	17	16	15	16	13	11	12
Total sleep time in Mins.	462	173	336	330	319	303	331	319	257	321	443	343	457	371	342	407

SLEEP AFTER NITRAZEPAM OVERDOSE

(PATENT NO. 4)

Number of Nights	20	21	22	24	25	26	27	30	32	35	38	40	41	43	45
Date	17/3	18/3	19/3	21/3	22/3	23/3	24/3	27/3	29/3	1/4	4/4	6/4	7/4	9/4	11/4
Delay to sleep Onset in Mins.	40	127	64	60	140	120	56	112	8	108	132	73	45	89	84
Delay to first rapid eye Movement (REM) Period in Mins.	47	10	42	51	31	19	127	48	53	45	45	50	123	60	52
REMS in first two hrs. of sleep in Mins.	22	44	19	22	20	40	-	12	21	18	11	1	-	22	11
WAKEFULNESS in Mins.	-	3	-	1	1	152	13	3	2	2	179	4	29	-	18
% Stage 1	2.3	5.3	1.3	3.1	2.6	8.9	6.1	2.6	8.5	7.6	7.8	4.4	5.0	2.9	3.2
% Stage 2	43.8	47.1	40.3	32.3	41.9	31.6	45.9	45.2	46.8	51.6	38.9	47.6	45.7	24.9	47.1
% Stage 3	10.5	6.8	9.5	9.7	10.9	4.2	3.8	7.5	5.9	2.4	11.8	11.0	5.1	17.2	5.7
% Stage 4	10.2	12.2	11.5	20.9	14.6	18.3	14.5	17.2	14.0	20.0	19.1	16.0	18.3	31.0	21.4
% REM Stage	33.2	28.6	37.4	34.0	30.0	37.0	29.7	27.5	24.8	18.4	22.4	21.0	25.9	24.0	22.6
Shift to W or Stage 1 in first two hrs. of sleep	13	8	10	8	6	7	9	8	6	7	6	7	8	5	7
Total sleep time in Mins.	458	401	435	435	495	242	419	378	415	309	239	361	436	358	409

SLEEP AFTER NITRAZEPAM AND PERPHENAZINE OVERDOSEPATIENT NO. 4 READMISSION

Number of Nights	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	17
Date	18/5	19/5	20/5	21/5	22/5	23/5	24/5	25/5	26/5	27/5	28/5	29/5	30/5	31/5	1/6	3/6
Delay to sleep in Minutes						179	79	103	49	100	51	47	152	331	100	48
Delay to first REM Period in Mins.						49	52	61	66	45	45	56	56	45	39	43
REMS in mins. during first 2 hrs. of sleep						19	11	72	37	25	15	39	19	21	27	21
WAKEFULNESS during Night in Mins.						-	-	-	1	-	-	1	6	-	7	-
% Stage 1						6.5	3.6	1.2	2.9	3.5	6.2	2.5	3.9	2.2	1.9	3.4
% Stage 2						43.2	42.0	33.9	34.8	43.7	44.8	40.8	24.6	23.3	45.8	30.3
% Stage 3						7.6	8.2	10.3	9.1	2.0	7.0	6.4	9.9	13.0	6.5	10.0
% Stage 4						15.5	17.9	20.3	13.8	12.7	13.5	11.5	27.6	24.5	11.3	27.2
% REM Stage						27.2	28.3	34.3	39.4	38.1	28.5	38.8	34.0	37.0	34.5	29.1
Shifts to W or Stage 1 in First two hrs. of sleep						8	10	13	17	15	12	14	13	15	12	15
Total sleep time in Mins.						254	383	347	328	383	408	451	279	499	430	443

DISCHARGED HOME

SLEEP AFTER NITRAZEPAM AND PERPHENAZINE OVERDOSE

PATIENT NO. 4

Number of Nights	18	20	21	23	24	27	29	30	31	33	34	35	36	37	39	41
Date	4/8	6/6	7/6	9/6	10/6	13/6	15/6	16/6	17/6	19/6	20/6	21/6	22/6	23/6	25/6	27/6
Delay to Sleep in Minutes	43	81	122	79	95	22	18	51	84	22	42	25	45	36	54	7
Delay to First REM Period in Mins.	39	51	52	53	60	59	49	58	51	46	64	63	39	49	55	50
REMS in Mins. during first two hrs. of sleep	30	21	15	18	42	20	11	8	14	8	12	13	15	2	9	21
WAKEFULNESS in Mins.	3	7	-	1	-	2	3	-	-	8	-	-	5	3	1	34
% Stage 1	2.7	5.9	5.6	4.6	2.9	2.8	3.4	2.4	2.7	5.8	3.9	4.4	4.8	3.6	1.6	2.6
% Stage 2	31.5	37.9	40.9	39.9	43.3	40.5	44.6	55.3	49.1	41.2	48.2	52.2	47.8	52.4	45.8	53.4
% Stage 3	9.8	16.0	3.1	6.9	7.2	4.4	6.0	11.2	5.4	10.5	6.4	3.4	3.0	8.7	2.5	9.9
% Stage 4	20.0	16.8	20.8	17.5	16.2	22.6	14.9	5.2	9.5	13.4	10.7	12.6	14.9	7.8	16.8	6.3
% REM Stage	30.0	23.4	23.6	31.1	30.4	28.7	31.1	25.9	33.3	29.1	30.8	27.4	29.5	26.5	33.3	27.0
Shift to W or Stage 1 in first two hrs. of sleep	13	12	14	13	12	11	10	9	12	11	12	10	9	11	6	5
Total sleep time in Minutes	437	372	333	365	273	393	389	389	415	441	388	497	380	396	397	312

SLEEP AFTER INTRAZEPAM OVERDOSE

(PATENT NO. 5)

Number of Nights	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Date	20/4	21/4	22/4	23/4	24/4	25/4	26/4	27/4	28/4	29/4	30/4	1/5	2/5	3/5	4/5	5/5	6/5	7/5
Delay to sleep in minutes			15	44	95	9	25	17	24	30	10	17	13	2				
Delay to First REM Period in Mins.		-	-	69	81	1	2	18	5	7	23	4	17	9				
REMS in Mins. during first two hrs. of sleep		15	3	22	49	51	44	27	7	41	6	5	13					
WAKEFULNESS during night in Mins.		9	7	88	144	158	178	222	138	143	197	79	80					
% Stage 1		7.4	5.7	8.9	11.0	4.2	6.7	13.5	15.2	13.4	11.5	8.6	14.3					
% Stage 2		92.6	75.7	42.3	36.6	30.9	30.5	33.9	32.6	33.8	32.4	40.4	50.2					
% Stage 3		-	-	10.9	4.4	2.9	11.7	2.0	2.9	4.5	13.9	6.9	5.7					
% Stage 4		-	-	11.0	14.9	16.0	25.1	14.8	19.6	19.8	17.8	16.4	18.0					
% REM Stage		-	-	7.6	23.0	32.0	26.0	35.8	29.7	23.5	24.4	27.7	11.8					
Shifts to W or Stage 1 in first 2 hrs. of sleep		16	18	22	20	25	21	20	24	21	23	19	20					
Total Sleep Time in Mins.		517	445	371	322	305	271	216	203	347	323	448	453					

SLEEP AFTER INTRAZEPAM OVERDOSE

(PATIENT NO. 5)

Number of Nights	20	22	24	25	27	29	30	31	32	34	37	38	39
Date	9/5	11/5	13/5	14/5	16/5	18/5	19/5	20/5	21/5	23/5	25/5	26/5	27/5
Delay in sleep in minutes	6	2	4	3	3	11	4	7	5	12	6	8	9
Delay in first REM period in mins.	5	7	10	11	14	6	6	8	15	2	41	47	9
REMS in Mins. during first two hrs. of sleep	20	33	32	24	36	38	23	26	14	43	8	19	19
WAKEFULNESS during nights in mins.	29	64	166	149	173	154	171	165	140	124	25	63	16
% Stage 1	10.5	2.9	4.6	4.0	3.0	3.6	3.6	5.8	4.0	11.6	4.6	4.2	3.0
% Stage 2	44.5	35.8	46.2	29.5	39.2	50.1	54.1	38.8	50.3	57.5	49.2	44.4	45.4
% Stage 3	22.1	13.8	6.7	12.9	10.7	13.5	10.0	13.5	11.3	3.7	16.2	14.2	16.4
% Stage 4	14.9	32.3	21.6	36.5	25.5	16.2	12.4	20.4	14.6	6.5	16.9	24.9	16.3
% REM Stage	9.9	14.7	20.9	17.1	21.6	16.6	14.9	21.5	19.8	20.7	13.1	12.3	18.9
Shifts to W or Stage 1 in first 2 hrs. of sleep	17	15	18	15	13	12	14	9	12	10	8	10	11
Total Sleep Time in Mins.	475	413	329	362	317	426	353	401	389	416	427	429	441

SLEEP AFTER PHENBARBITONE OVERDOSE

(PATENT NO. 6)

Number of Nights	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Date	8/3	9/3	10/3	11/3	12/3	13/3	14/3	15/3	16/3	17/3	18/3	19/3	20/3	21/3	22/3	23/3	24/3
Delay to sleep in Minutes			C O M A														
Delay to First REM Period in Mins.					5	32	14	17	20	18	26	23	23	25	25	25	25
REMS in Mins. during first two hrs. of sleep					64	50	62	41	72	38	42	43	43	43	43	43	43
WAKEFULNESS during night in Mins.					1	12	8	12	14	40	49	37	37	37	37	37	37
% Stage 1					6	8	2	3	6	6	11	9	9	9	9	9	9
% Stage 2					8.1	7.6	9.3	4.3	6.9	4.7	4.4	2.8	2.8	2.8	2.8	2.8	2.8
% Stage 3					68.7	61.2	60.0	52.4	57.8	39.5	46.4	36.8	36.8	36.8	36.8	36.8	36.8
% Stage 4					15.5	10.1	6.2	9.9	9.0	7.2	7.5	8.3	8.3	8.3	8.3	8.3	8.3
% REM Stage					-	0.7	-	-	0.9	11.6	11.5	15.6	15.6	15.6	15.6	15.6	15.6
Shifts to W or Stage 1 in first two hrs. of sleep					7.7	20.4	24.5	33.4	25.4	37.0	30.2	36.5	36.5	36.5	36.5	36.5	36.5
Total sleep time in Mins.					16	19	25	29	28	36	32	37	37	37	37	37	37
					509	458	452	446	479	489	399	387	387	387	387	387	387

SLEEP AFTER SODIUM AMYLOBARBITONE OVERDOSE

(PATENT NO. 7)

Number of Nights	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Date	7/6	8/6	9/6	10/6	11/6	12/6	13/6	14/6	15/6	16/6	17/6	18/6	19/6	20/6	21/6	22/6	23/6
Delay to sleep in Minutes				37	41	60	46	46	26	26	43	32	15	18			
Delay to First REM period in Mins.				57	56	47	73	73	64	32	59	45	49	33			
REMS in Mins, during first two hrs. of sleep				25	3	5	6	6	7	14	9	4	16	10			
WAKEFULNESS in Mins.				5	-	1	-	-	-	-	-	-	-	-			
% Stage 1				8.6	3.6	5.2	5.4	3.8	2.1	2.1	4.4	4.1	2.3	2.6			
% Stage 2				44.2	43.5	34.3	47.7	34.6	38.8	38.8	37.9	31.0	36.2	36.5			
% Stage 3				6.6	8.0	7.8	9.3	12.7	15.8	15.8	14.1	7.2	11.6	16.2			
% Stage 4				20.4	18.0	22.3	14.7	30.0	19.7	19.7	22.5	35.6	30.6	24.5			
% REM Stage				20.2	26.9	30.4	22.9	18.9	23.6	23.6	21.1	22.1	19.3	20.2			
Shift to W or Stage 1 in first two hrs. of sleep				14	17	20	18	13	16	16	12	7	4	6			
Total sleep time in Mins.				441	459	396	437	427	453	453	456	457	458	436			

SLEEP AFTER SODIUM PENTOBARBITONE OVERDOSE

(PATIENT NO. 2)

Number of Nights	1	2	3	4	5	6	7
Date	29/3	30/3	31/3	1/4	2/4		
Delay to sleep in Minutes			25	173	82		
Delay in First REM period in Mins.			24	26	29		
REMS in Mins. during first two hrs. of sleep			39	43	45		
WAKEFULNESS during night in Mins.			12	10	14		
% Stage 1			14.5	17.0	7.6		
% Stage 2			53.7	45.4	32.0		
% Stage 3			3.3	5.5	9.2		
% Stage 4			3.6	2.7	6.4		
% REM Stage			19.9	28.4	37.8		
Shifts to W or Stage 1 in first two hrs. of sleep			310	192	224		
Total sleep time in Mins.			359	199	392		

UNCONSCIOUS

SLEEP AFTER ASPIRIN OVERDOSE

(PATENT NO. 10)

Number of Nights	1	2	3	4	5	6	7	8	9	10	11	12
Date	3/6	4/6	5/6	6/6	7/6	8/6	9/6	10/6	11/6	12/6		
Delay to sleep in Minutes	-	-	-	36	55	50	73		23	46		
Delay to first REM Period in Mins.	-	-	-	53	52	42	39		51	47		
REMS in Mins. during first two hrs. of sleep	-	-	-	6	21	19	31		11	20		
WAKEFULNESS during night in Mins.	-	-	-	-	-	-	-		-	-		
% Stage 1	-	-	-	4.6	4.5	3.2	4.2		4.2	2.4		
% Stage 2	-	-	-	39.6	36.8	38.4	51.8		49.6	48.4		
% Stage 3	-	-	-	11.1	8.9	10.6	3.0		5.3	6.6		
% Stage 4	-	-	-	26.9	21.0	20.7	16.1		14.9	14.2		
% REM Stage	-	-	-	17.8	28.8	28.7	24.9		28.0	28.4		
Shifts to W or Stage 1 first two hrs. of sleep	-	-	-	7	9	10	8		6	6		
Total sleep time in Mins.	-	-	-	476	401	447	388		474	428		

HAD SEVERE PRE-MENSTRUAL PAIN

SLEEP AFTER FENFLURAMINE OVERDOSE

(PATIENT NO. 11)

Number of Nights	1	2	3	4	5	6	8	9	11	12	14	15	19
Date	15/7	16/7	17/7	18/7	19/7	20/7	22/7	23/7	25/7	26/7	28/7	29/7	2/8
Delay to Sleep in Minutes			13	18	37	7	7	23	33	28	21	16	33
Delay to First REM Period in Mins.	0		0	45	52	49	53	50	48	91	82	51	65
REMS in Mins. during first two hrs. of sleep	22	11	31	7	7	7	22	11	9	15	16	7	4
WAKEFULNESS during Night in Mins.	1	-	23	5	5	5	-	20	-	10	-	-	4
% Stage 1	4.9	6.3	9.6	4.3	4.3	4.3	7.4	5.9	5.3	4.1	4.6	3.2	3.4
% Stage 2	52.9	43.9	46.6	39.8	39.8	39.8	50.2	44.8	45.4	46.7	46.0	48.4	49.5
% Stage 3	4.1	8.7	3.6	9.0	9.0	9.0	3.8	9.5	8.8	7.6	9.1	10.5	7.6
% Stage 4	8.0	16.7	17.1	19.6	19.6	19.6	15.8	19.6	16.3	15.8	13.6	14.8	18.7
% REM Stage	29.8	24.1	22.8	27.1	27.1	27.1	22.9	20.2	24.2	25.8	26.7	23.1	20.8
Shifts to W or Stage 1 in first two hrs. of sleep	3	7	6	5	5	5	9	8	8	7	8	9	6
Total Sleep time in Mins.	480	502	490	485	485	485	453	474	465	449	471	475	463

SLEEP AFTER FENFLURAMINE OVERDOSE

(PATIENT NO. 12)

Number of Nights	*1	*2	3	4	6	7	11
Date	23/7	24/7	25/7	26/7	28/7	29/7	2/8
Delay to sleep in Mins.	-	-	24	16	18	6	20
Delay to First REM Period in Mins.	-	260	66	46	52	87	71
REMS in Mins. during first two hrs. of sleep	-	-	4	12	31	10	3
WAKEFULNESS during Night in Mins.	-	-	8	10	6	-	2
% Stage 1	40	28.0	5.9	4.8	5.1	3.8	3.4
% Stage 2	60	51.4	37.3	35.2	35.9	41.8	51.3
% Stage 3	-	20.0	10.4	13.5	12.6	11.5	9.7
% Stage 4	--	-	19.6	18.9	18.4	16.6	14.8
% Stage REM	-	0.6	26.8	27.6	28.0	26.3	20.8
Shifts to W or Stage 1 in first two hrs. of sleep	-	-	8	6	4	3	5
Total sleep time in Mins.	*95	*340	482	508	484	472	477

* only part of night's sleep recorded (see text).

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